they are not due to negligence. It is just bad luck if such a result occurs, and it has to be accepted as one of the hazards of being ill or being treated. No one pays compensation for such occurrences.

Finally, there are the completely unpredictable complications that have not been described before, or are so rare that no ordinary doctor can be expected to know about them. No one pays compensation for them because it is not possible to anticipate an unknown danger. Unpredictable events are naturally more common with new treatments than with the old. Should they occur often enough to be known, they become matters of negligence if they are preventable, or inevitable hazards if they are not.

In therapeutic research, the question we have to decide is whether it is really so different from clinical medicine that we need a special method to deal with claims. After all, any treatment even as simple as giving an antacid for stomachache is, to some extent, experimental. If we move through treatments where the outcome is increasingly uncertain, we arrive at the extreme of the formal clinical trial. Is it now clear that therapeutic research is something different; and, if so, in what respect is it different? The difference cannot lie in the novelty of the treatment because new methods have always been tried without any suggestion that this takes one outside the field of clinical medicine. It must be because doctors are using special scientific methods to make more than usually certain that their conclusions are valid. I see no reason why this should be allowed to obscure the obvious fact that we are still treating ill patients. As far as claims are concerned, I see no essential difference between therapeutic research and clinical practice.

But there are doubts about this matter. Many doctors who are about to run a clinical trial do believe that there is something different, or fear that there may be, and rightly suspect that the public will be more impressed by the experiment than by the treatment. On these grounds alone they have good reason to inquire. It must also be admitted that what the patient can agree to is different in medical practice than in a clinical trial. The patient should have at least some choice between having a new treatment or sticking to the old in clinical practice. But in the clinical trial this choice is decided by those who run the trial. All that the patient can decide is whether to submit to what the investigator chooses.

In nontherapeutic research the situation is different. There is no possible benefit to be weighed against possible damage; anything that goes wrong is clearly entirely on the debit side. One of the matters on which the college conference was most firm was that any debt to the "guinea pig" must be paid quickly and without argument. The matter was viewed as one of professional ethics because, although doctors in this situation are acting as scientific inquirers, they are still members of a profession that accepts responsibility for those with whom it deals. I am sure there would be a storm of outrage if a

claim were rebutted on grounds such as the fact that the subject had voluntarily accepted the risk. There is also the matter of expediency: the supply of volunteers would rapidly dry up if it were known that compensation is not paid or is difficult to obtain.

I shall now review the sources of damage to see what difference there is between compensation for "guinea pigs" on the one hand and patients and subjects of therapeutic research on the other. The message is that the defense societies will not pay damages in all the cases where they should be received.

Damage from negligence would be compensated by the defense societies in whatever form it occurred. Research work is accepted as a proper activity of doctors. The attitude of the law toward negligence in research is the same as for clinical medicine, and so is that of the defense societies. Here one thinks of inexcusable mistakes, such as injecting potassium intravenously instead of sodium, or cleaning the skin with a corrosive fluid. When we move on to negligence due to failure to obtain valid consent, we are dealing with a matter that is likely to be much more prominent in "guinea pigs" than in patients; it is already a matter of public concern. It is also much more complicated, bedeviled by such questions as whether all "guinea pigs" must be volunteers. And if not, how far can the investigator go? And if so, who, if anyone can give consent on behalf of a person who does not have the capacity because of age or infirmity?

I shall not discuss these matters because it is not my task. But I can point out this still constitutes the matter of valid consent with which we are familiar in clinical medicine, although it is clear that warning of possible risks is much more important with "guinea pigs" than it is with patients. For the defense societies, the question of liability would turn on whether the research worker was negligent in dealing with the situation. If so, we would pay for the consequences.

Next comes the question of normal hazards, such as arterial thrombosis from a catheter. Although these dangers have to be tolerated by patients, there is no reason why "guinea pigs" should put up with them at all because their only prospect of a compensating advantage has been their hope and belief that they may be doing good to humanity. Such altruism may be enough to prevent their making claims, but if not, does the liability fall on the defense societies? The answer is a very firm "no," for it cannot be said that the doctor was negligent when there is nothing to be done to avoid the damage.

There is also the possibility of unpredictable damage. Although we have never had such a claim arising from nontherapeutic research, the sort of hazard I am thinking of is perhaps sufficiently indicated by the troubles that arose from thalidomide or the beta-blocker practolol. If such a claim were made, it is likely that it would come to a defense society in the first instance. I am sure that it would be rebutted because failure to anticipate a danger that was as yet unknown could not be considered negligent.

The defense societies pay compensation only for negligence because the only power the courts have to compel a doctor to pay damages stems from negligence. It is this power that called the defense societies into existence. Virtually all our experience is in clinical medicine so far but we are prepared to do the same for our members in all forms of research and, indeed, could be compelled to do so. We do not and obviously could not operate a no-fault scheme in clinical medicine for all the ills that arise from disease or attempts to cure it, and we are not prepared to make a voluntary exception for research.

Yet no-fault compensation is exactly what we all agree should be paid to "guinea pigs." What is the alternative course?

The meeting at the Royal College took the view that any organization that promoted nontherapeutic research should also accept responsibility for damages, which seems reasonable. The financial burden would be trivial compared with what is spent on research, as is clear from a consideration of how unlikely it is for a claim to arise and from the scale of damages set by the courts. Representatives of research bodies were at the meeting, and they did not disagree with this suggestion. It is difficult for me to say how far it has permeated the large number of organizations that promote research and whether they all agree or would still agree when presented with a claim. But the view of the two largest, the Medical Research Council and the National Health Service, is clear. It is that an *ex gratia* payment would be sympathetically considered, although it is not possible to give a general undertaking. Each group has, in fact, made one payment on this basis.

The scheme is simple enough to understand: those who need compensation get it, and those who have to pay it know their obligations. But I must emphasize that it is notional. We have no experience in therapeutic research, and in nontherapeutic research it is minimal. There will be no accepted routine until enough cases arise that have to be dealt with. Nevertheless I think that the defense societies, which occupy a central position here, will try to push it in the way I have described.

It would be wrong to end on such a satisfied note without saying something about probable causes of dispute. There certainly will be disputes because a graded series of events has been divided into categories, categories create boundaries, and where there are boundaries there can always be argument about which is the right side for a given case. The important boundary here is between negligence and no negligence. The defense societies are used to dealing with this in clinical medicine. But the parties to the dispute will not be the same in therapeutic and nontherapeutic research. In the former the patient is, in effect, claiming from a defense society in the usual way. In nontherapeutic research the "guinea pig" only has to demonstrate damage to get his no-fault compensation. An argument about negligence would then be between a defense society and a research fund; the "guinea pig" should not be brought into it at all. Any argument should be in private and settled quickly lest suspicions

grow that the doctors did not know what they were about or that the prospect of compensation was uncertain.

There could also be arguments about quantum, which are usually settled by bargaining between counsel. If the two sides cannot agree, they go to court for a settlement. In the United Kingdom cases of civil negligence are not tried with a jury. The judge both gives a verdict and decides the sum. Plaintiff's counsel does not name the sum hoped for but is confined to describing the pain and suffering, pointing out how much earnings were lost by an illness, and so on. Such a system is fairly predictable, and it is part of counsel's job to let clients know what a judge might say. This is how damages would be settled for negligence, but I hope that the defense societies would be inclined toward generosity in the case of "guinea pigs." A "guinea pig" damaged without negligence would have no right of action in the courts; again I can only hope that an *ex gratia* payment by a research body would be as ungrudging as we should like it to be.

There is also the possibility that a "guinea pig" might believe that an experiment had made an existing illness worse or caused one to be contracted soon after. This would be a sad affair because the intention to protect and help the "guinea pig" would turn to refusal and even hostility.

After all this speculation I shall now describe the five known cases.

1. Nontherapeutic experiment on a healthy volunteer: The skin of the anticubital fossa was burned by the wrong cleaning solution. Defense society paid on grounds of negligence.
2. Nontherapeutic experiment on a baby: The doctor was doing a series of observations on the capillary circulation of the nail bed. He burned a finger with the heat of the lamp. Defense society paid on grounds of negligence. It is to be noted that these experiments were unlawful because no one in the United Kingdom can give valid consent on behalf of an infant. But this point was not raised.
3. Nontherapeutic experiment on a volunteer patient: Radial artery thrombosed by a catheter. All three defense societies had a member concerned. The work was promoted by a university, and there was no negligence. The Scottish society refused to contribute on principle because it held that the university was responsible. The university was covered by an insurance company that did not share our views on the necessity of prompt compensation for "guinea pigs." The other two societies agreed with the Scottish but decided to pay the damages to stop the argument. This was the case that decided us to ask the Royal College of Physicians to call a meeting.
4. Nontherapeutic experiment on a volunteer patient: Another endarterial catheter thrombosis. Defense society rebutted the claim as there was no negligence. It went further and drew the

research body's attention to the views of the Royal College of Physicians. Nothing more was heard, and I assume that no-fault compensation was paid.

5. A case compensated by the Medical Research Council with no application to a defense society: I have no details, but it was presumably damage sustained in a nontherapeutic experiment.

In conclusion, it seems that things are going according to plan.

As a postscript, I must report on a recent case reported by the Royal Commission on Civil Liability and Compensation for Personal Injury. The commissioners made two comments relevant to my theme:

1. In nontherapeutic research they said: "We think that it is wrong that a person who exposes himself to some risk in the interests of the community should have to rely on *ex gratia* compensation in the event of injury." They accordingly recommended that "guinea pigs" should have a right of action for any damage they suffer.

2. They also recommend that a volunteer in a clinical trial should have a right of compensation from those who organized the trial.

That might do no more than extend the existing practice because drug companies already feel compelled by public opinion to make *ex gratia* payments if there is damage on a grand scale. But from the commissioners' comments it seems to me that they do not recognize the clean distinction between therapeutic and nontherapeutic research and have, therefore, destroyed that boundary. Where is the new boundary to be erected? By implication it is between what is orthodox and what is new. This is ominous, and I can foresee the possibility of the courts inching that boundary away from the formal clinical trial, approaching the point where any doctor treating a patient in a way that has not been done many times before will be liable for damages. Such a trend would have been applauded by the later Pharaohs, but it did fossilize their medicine.

COMPENSATION OF RESEARCH SUBJECTS FOR ADVERSE EFFECTS

Seymour Perry

An HEW Secretary's task force on compensation of injured research subjects come to the following conclusions:

1. Volunteer subjects in biomedical and behavioral research should be compensated if they are injured in the course of participation in research conducted or supported by HEW. Malpractice or negligence in this context is not a consideration; other mechanisms are available to deal with such injuries.
2. It is not useful, for this purpose, to distinguish between injuries arising in the course of therapeutic or nontherapeutic research.
3. Injuries that should be compensated include "harm, disability, or death, suffered by a subject of research where such injury is:
   a. "proximately caused by such research, and
   b. "on balance exceeds that reasonably associated with illness from which the subject may be suffering and with treatments usually associated with such illnesses at the time the subject began participation in the research." Thus, all normal volunteers would be compensated for injury.
4. Compensation should cover loss of income and medical expenses, but not pain or suffering unless earning capacity is adversely affected.
5. The preferred mechanism of compensation is that of insurance at the institutional level through private carriers, self insurance, or a pool arrangement. Premiums would be chargeable to indirect costs.*

*In June 1977 the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research endorsed the recommendations of the task force; in addition, the Commission urged that coverage should be assured "for research which is not Federally funded and for research that is regulated under the Federal Food, Drug, and Cosmetic Act." The Commission also asked that informed consent documents should contain information concerning compensation where such a mechanism exists, or in the absence of such a mechanism, the volunteer would have to bear the cost of any injury. The task force concurred with this latter recommendation.

The issue of compensation of injured research subjects has been under consideration at various times in the Department of Health, Education, and Welfare for nearly a decade. A number of approaches have been proposed; however, none has been accepted since the social implications are difficult to assess and there were no data upon which to base fiscal estimates.

Volunteers injured in the course of research supported or conducted by the Public Health Service have no legal recourse to seek compensation unless the injury can be traced to negligence or product liability. Through the years there has developed a set of regulations now codified as Part 46 of Title 45 of the Code of Federal Regulations aimed at protecting the rights of individuals and providing for their safety to the extent possible in clinical research. However, even with the best of controls and safeguards, individuals participating in research are injured, and, although the vast majority of medical institutions will provide care for acute injury, it is the exception when long-term care is available to the volunteer who sustains a chronic injury. Furthermore, there is no mechanism to compensate the individual for lost wages or earning capacity. If a volunteer has third-party coverage, his medical expenses may, in part at least, be covered; but generally there is no reimbursement for loss of income.

One notable exception to this situation exists at the University of Washington, which does provide for compensation in the event of research-associated injury. Since 1972 the university has carried insurance for human subjects who are injured in the course of research; insurance is provided by a private carrier with coverage patterned after the workmen's compensation program in the State of Washington. The policy provides compensation covering the actual cost of the medical treatment, of lost wages, and other identifiable expenses connected with unanticipated adverse effects. The policy does not cover children, and volunteers are generally not informed that there is such insurance prior to injury. Approximately 180,000 individuals have been covered from 1972 through 1977 at an annual premium of $35,000. To the present time there have been 15 claims; 14 have been awarded, and no settlement has exceeded $1,500. There is no formal arbitration process, but claims are settled by agreement among the claimant, the investigator, and the insurance carrier.

The issue of compensation began to receive increased attention as concern mounted in the early 1970's over the rights and welfare of volunteers participating in clinical research. That, in turn, led to strengthening informed consent documents and to requirements for establishment of institutional review groups with carefully defined composition and responsibilities. But it took an incident in Boston in 1974 to force action on the part of the Federal Government.

The guardian of a 6-year-old child who was under consideration as a marrow donor for her 10-year-old sibling raised some questions as to the availability of medical care should the donor sustain some unanticipated adverse reaction not attributable to negligence. During court hearings, it was revealed that in the

absence of negligence there existed no provision to compensate either the donor or her parents should an injury occur. Within a short period of time, two additional court cases concerning the same issue occurred. The situation was ultimately settled when the institution involved was able to obtain short-term coverage, with the premiums charged to research grants under which the marrow aspirations were to be performed. It is of interest that the policy that was finally written (and is still in effect) was a no-fault policy with $250,000 coverage per event and with a premium of $100 per volunteer.

This event was a major factor which led the then Assistant Secretary of Health, Theodore Cooper, to urge the then Secretary of HEW, Caspar Weinberger, to authorize a study of the entire issue. Accordingly, in early 1975, the Secretary appointed an HEW task force with the NIH as the lead agency[1]. Law, medicine, and ethics were represented on the task force, which held its first meeting in May 1975 and subsequently held 24 half-day meetings during the succeeding 18 months[2].

The questions confronting the task force were:

1. Should individuals participating as subjects of biomedical research supported or conducted by HEW be compensated for injury arising directly out of such research? Does society, which benefits from such research, have a moral obligation to compensate those injured?
2. If so, which classes of research subjects, therapeutic or non-therapeutic, should be compensated?
3. What types of injury should be compensated?
4. What should the mechanism be for compensation?
5. What process should be followed in compensation?

Specifically, the issues that had to be assessed included:

1. Socioethical and moral obligations of the Federal Government.
2. The legal authority of HEW to require compensation or the assurance of compensation.
3. The incidence of research-related injuries among volunteers.
4. Existing Federal mechanisms for compensation or indemnification.
5. Possible alternative mechanisms for compensation if the task force were to take the position that injured research subjects should be compensated.

To assist the task force in its mission, testimony was solicited from ethicists, clinical investigators, economists, and lawyers knowledgeable in this area; and studies were commissioned dealing with the legal, ethical, economic, and actuarial aspects of the questions and issues confronting the group.

Socioethical and Moral Obligations of the Federal Government

Unquestionably, the key issue concerning the task force was that of the Government's responsibility to provide compensation to volunteers inadvertently injured in the course of their participation in federally supported or conducted research. From the standpoint of fundamental justice and in the context of research, there appear to be three types of justice:

1. Distributive—Both the benefits and burdens of the given activity are distributed over a wide segment of society. This type of justice applies in research whereby individuals in large segments of the population are both subjects and beneficiaries of the research.
2. Reparative—There is an attempt to assign fault in case of injury and then to assess the responsibility of the party at fault to make amends for the injury. This clearly involves deliberate or negligent injury and provides the basis for tort law.
3. Compensatory—Here, amends are made for injury even in the absence of fault or assignment of responsibility for injury.

After extensive discussion and deliberation along with consideration of the opinions of consultants in ethics and law, the task force concluded that society, through the Federal Government, is obliged to make amends for an injury that arises from an activity aimed at benefiting the whole of society. Since society requires and sponsors the research and also is the beneficiary of such research, compensatory justice warrants the redress of injury suffered by persons who are volunteers in such research.

Delineating the limits of the Government's obligation to injured research subjects, particularly those involved in therapeutic research, posed a very difficult issue for the task force. The key question was: Does the volunteer abrogate the right to compensation for injury by virtue of the fact that he has volunteered? Once the task force came to the position that the individual does not lose the right to compensation for injury because of the act of volunteering, it was clear that normal individuals, who do not stand to benefit from the research themselves, should have the right to compensation. On the other hand, an individual volunteering for therapeutic research has an opportunity to benefit personally, which raises a much more complex question. In therapeutic research, it may be difficult to distinguish between the side effects of treatment and the disease process itself, and unavoidable side effects may occur not only in experimental treatments but also in standard therapy.

The task force resolved the issue to its satisfaction by concluding that the distinction between therapeutic and nontherapeutic research is not useful and would greatly complicate the matter. It followed that when injury was proximately caused by research, compensation is clearly indicated. However,

the type of injuries to be compensated presented extraordinarily complex and difficult questions. After several long and vigorous debates, the task force adopted the position that an injury should be compensated if "on balance [it] exceeds that reasonably associated with such illness from which the subject may be suffering, as well as with treatment usually associated with such illness at the time the subject began participation in the research."

Legal Authority of HEW To Require Compensation

Current regulations require grantee and contractor institutions to provide safeguards for the rights and welfare of subjects at risk in research. Properly constituted institutional review groups must be established with responsibility for reviewing research protocols submitted by investigators prior to implementation. Currently, the institution must provide assurance that this process is being followed in all research supported by the Federal Government. An extension of this system, designed to protect human subjects and to provide for inadvertent injury to volunteers participating in research, appears logical and legally acceptable.

Incidence of Research-Related Injuries Among Volunteers

The task force recognized from the beginning that recommendations for compensation would not be acceptable to those who had to make the final decisions. With some uncertainty as to chances of success and apprehension over the effort itself, especially in view of existing concerns over possible malpractice allegations, the task force designed and implemented a trial survey of a small number of clinical investigators. The results of this trial (published in 1977) suggested that investigators would respond candidly and that a larger survey could be undertaken with some confidence. Three hundred and thirty-one investigators were then selected at random from computer files in the NIH Division of Research Grants, reflecting more than 130,000 subjects, including about 40,000 in therapeutic and 93,000 in nontherapeutic research conducted during the previous 3 years. These investigators were sent a survey questionnaire aimed at an assessment of the incidence of both nontherapeutic and therapeutic injuries of various types.

The survey revealed that among the 93,000 individuals who had participated in nontherapeutic research, there were 37 temporary disabilities, 1 permanent disability, and no fatalities. In the 40,000 individuals who had participated in therapeutic research, there were 937 temporary disabilities, 13 permanent disabilities, and 43 fatalities. Thirty-seven of the 43 fatalities were reported to have received chemotherapy for cancer. Further analysis of the data (by Dr. Philippe Cardon, associate director, Clinical Center, NIH) suggested that the risks of nontherapeutic research did not exceed the risks associated

with everyday existence; in therapeutic research, the risks were no greater than treatment in other settings[3].

The task force was cognizant of the problems associated with this survey: the accuracy of reporting was uncertain; individual investigator biases as to what constituted injury could not be assessed, etc. It should also be noted that the incidence of injuries reported in the survey is obviously not equivalent to what might be the incidence of compensable injuries. Nevertheless, the incidence of injuries reported in the survey seemed to confirm the general impression of clinicians on the task force and others that serious injury is not a common occurrence in the course of research on volunteers conducted under existing guidelines and safeguards.

Existing Federal Mechanisms for Compensation or Indemnification

Having concluded that society and the Federal Government have an obligation to compensate individuals for injuries as defined above, the task force proceeded to examine existing Federal mechanisms of compensation. Detailed studies of the Federal Employees Compensation Act (FECA), the Black Lung Act, the Veterans Administration Compensation Act, and the Flood Insurance Program were conducted. In addition, possible legislative mechanisms for compensation and foreign efforts in this area were also examined. No good international model for this country was identified, although in some countries there are mechanisms for compensation that are usually incorporated into a larger scheme of social welfare, national health insurance, and workmen's compensation.

Of the Federal mechanisms assessed, it appeared that FECA provides the most useful model for compensating injured research subjects. It is a no-fault insurance program covering work-related injuries and generally provides compensation for medical expenses, disability, and lost wages. Compensation is not provided for "pain and suffering" as such, unless earning capacity is adversely affected. However, for FECA to be applicable to research subjects, legislative amendments would be required. It should be noted that state workmen's compensation laws do not, in general, provide coverage for research injuries.

Possible Alternative Mechanisms for Providing Compensation

The task force solicited proposals for compensation mechanisms from experts in law, economics, and actuarial science. Each expert was asked to address (1) the factual basis for implementation, (2) potential problems in administration, (3) the nature of the Federal role, (4) additional compensation mechanisms judged suitable, and (5) expected performance of each mechanism during periods of large and small numbers of claims. The task force recognized that different mechanisms might be utilized for research *conducted*

by the Government as opposed to research *sponsored* by the Federal Government. It quickly became obvious that FECA or a newly legislated program would be necessary for research conducted by the Federal Government since other forms of insurance (e.g., private insurance) were not accessible to Federal employees for this purpose.

Insurance mechanisms (other than Federal) suggested by commissioned studies included a private insurance system with Federal underwriting on uninsurable risks and a compensation mechanism created by regulation rather than legislation. Modification of FECA was also suggested to include a deductible coverage under which research institutions would meet certain initial medical expenses and other costs incurred by research injuries.

The task force concluded that the insurance mechanism of choice was private insurance. It presents a number of advantages that make it preferable to insurance schemes that might be put in place by legislation. These include fixing responsibility at the local level, allowing for interaction between the institution and the principal investigator directly, and permitting the development of an insurance "package," of convenient size, perhaps as part of the general liability insurance that all institutions carry. Coverage can be readily extended to non-Federal research in the same institution and to mandated research. The form private insurance might take is flexible, including self-insurance (particularly by large institutions), insurance pools, and coverage provided by insurance carriers.

However, programs requiring legislation, whether modification of FECA or special legislation, would provide an important advantage. FECA is a mechanism already in place, and special legislation has a precedent (i.e., FECA) recognized as working reasonably well. Furthermore, a legislated program would probably be less expensive. However, legislation might require years to enact. It would also be complex; it would need to encompass children and would have implications for other parts of FECA and for other agencies (e.g., the Department of Defense) and would not be applicable to research supported by private sources (e.g., foundations). For research conducted directly by the National Institutes of Health or by the Alcohol, Drug Abuse, and Mental Health Administration, modification of FECA or, alternatively, special legislation would provide the only legal recourse since private insurance cannot legally be utilized by these agencies. It should also be pointed out that the legal basis for requiring compensation in regulated research is not clear. This is an issue that will have to be addressed separately.

The task force recognized that in any case a compensation requirement, regardless of the mechanism, would place an additional burden on research institutions over the substantial legal obligations already imposed on these organizations. However, the sensitivity in American society about the ethics of human experimentation is such that this is an issue that can no longer be ignored. An additional concern arises from the possibility that the availability of compensation would stimulate large numbers of claims, although under the

narrow definition of injury adopted by the task force and based on results of the survey, compensable injuries should be relatively small. Yet, it is possible that the mere availability of compensation may generate large numbers of claims.

Having come to the conclusion that private insurance was the preferred compensation mechanism, the task force began to explore this possibility with the insurance industry. Letters were sent by the Assistant Secretary of Health to 27 insurance carriers and 5 insurance alliances to elicit formal reactions. It soon became obvious that there were two factors that cast uncertainty on the possibility of private insurance: (1) anxiety in the insurance industry over the absence of previous experience in coverage of research subjects (despite the data from the University of Washington), and (2) weakness in the economy, specifically, financial weakness in the insurance industry itself. At the same time, it was also obvious that a federally administered program of compensation, as an alternative, was viewed with some apprehension by the industry. In brief, there was little or no indication of firm interest by insurance carriers in response to the inquiries on behalf of the task force.

The group felt that at this point in its deliberations it had gone as far as it could and that its charge had been fulfilled. However, in view of the remaining uncertainty concerning the mechanism of insurance, the task force recommended to HEW that a "Notice of Proposed Rulemaking" be published in the *Federal Register* to elicit opinions of the research community and to obtain formal reactions from the private insurance industry.

With publication of the task force report, although the recommendations were not to be acted on for some time for a variety of reasons, it appeared obvious to many that societal concerns would inevitably force action if federally supported clinical research is to continue. This prediction seems to have been borne out, and the initial actions aimed at implementing the recommendations are about to be set in motion.

Notes

1. The author wishes to emphasize that much of this presentation is drawn from the deliberations of the task force and from its report.
2. For copies of the report of the task force, "HEW Secretary's Task Force on the Compensation of Injured Research Subjects" and the appendixes, contact: National Institutes of Health, OD/OPPE/DRA, Building 31, Room 1-B-58, Bethesda, Maryland 20205.
3. The survey and the analysis of the data obtained were published: Cardon, P.V., F.W. Dommel, Jr., and R.R. Trumble (1976). Injuries to research subjects, a survey of investigators. N Eng J Med 295:650-654.

DISCUSSION

F. William Dommel

The presentations by Dr. Harman and Dr. Perry provoked an active discussion that focused primarily on the following issues:

A question was raised as to the appropriateness of not informing subjects of research as to the availability of a no-fault compensation mechanism in the event of a research-related injury. Most agreed that prospective subjects of research should be so apprised. A case in point is that at least one Institute within NIH has been advised by one of its review bodies that in the future they will insist on proof of such notification. It was also remarked that *The Health, Education, and Welfare Secretary's Task Force on the Compensation of Injured Research Subjects*, of which Dr. Perry was the chairman, also recommended such notification.

The difficulty in distinguishing between therapeutic and nontherapeutic research procedures was discussed. It was argued that in light of this difficulty a compensation mechanism that would afford benefits only to those injured by therapeutic procedures would incur serious definitional problems. A minority view, however, was that even though the two categories (therapeutic and nontherapeutic) do indeed merge, there is in practice a clearly identifiable distinction between them when judged by the physician-researcher.

A further question discussed was: Should the availability of compensation in the event of injury be influenced if a research subject is paid for his participation? It was generally agreed that compensation should not be dependent on whether there had been payment to a volunteer. It was mentioned that the payment of volunteers for their participation in research does raise an ethical issue in itself under most circumstances.

The Royal Commission report concerning compensation for research-related injuries (about which Dr. Harman spoke) was a further discussion topic. He mentioned that this particular report only speaks to product liability and does not address the topic of medical service injuries in research. Some agreed that it would seem proper that compensation for injuries occurring in the course of testing new drugs should be provided by the drug manufacturer, as the Royal Commission recommended. However, contrary to the Royal Commission's recommendations, it was suggested that the drug manufacturer should not be responsible for medical treatment injuries occurring in the course of additional testing (not conducted by the manufacturer) of an already licensed drug. Some thought that it may have been a mistake that the Royal Commission made no provision for compensating medical service injuries in research. Noting the fact that malpractice insurance fees and the number of malpractice claims have been rising at a high rate, some felt it likely that claims

against researchers might follow the same course once it is known that compensation is available. There was some agreement with this point, but generally it was felt that we really will not know the answer until a compensation program can be enacted and the results reviewed. Dr. Perry mentioned that the compensation program recommended by the HEW secretary's task force studying compensation would be a no-fault program and would not require adjudication in the courts. The task force expected only a small number of valid claims once the mechanism was in place. Dr. Perry noted further that there had been some experience with the operation of a compensation mechanism at the University of Washington and that very few claims had been made during the more than 5 years of the program. The university's experience, however, cannot be used to predict assuredly the number of claims that might arise elsewhere since the volunteers were not advised that compensation might be provided if they were injured in the course of the research program.

Dr. Harman was asked if nonmedical (nonphysician) personnel were eligible for membership in the defense society in the United Kingdom and through this membership to be insured against injuries judgments. Dr. Harman said that to the best of his knowledge nonmedical persons were eligible and would need only to apply for membership.

One commentator expressed his concern about the lack of available insurance for research injury in the United States today. He noted that he had been unsuccessful in seeking such coverage and, in fact, had found only one carrier that was insuring one large-scale clinical trial in only one city in the United States. In the search Lloyd's of London agreed to provide such coverage, but the cost would have been prohibitive. At this point, Dr. Perry noted that in late 1976 the Assistant Secretary for Health, HEW, at the request of the task force, had contacted 27 insurance carriers and 5 insurance alliances seeking no-fault insurance coverage for injuries in HEW-supported research. Nine carriers had no interest, nine were slightly interested, and nine wanted to study it further. However, institutions with other insurance companies might be more successful in their contacts with them. The University of Washington no-fault insurance compensation coverage has been a moneymaker for the Aetna Life and Casualty Company.

The discussion centered once again on the kind of research that should offer compensation to those who are injured while participating. It was expressed that there is a great similarity between therapeutic and nontherapeutic research, in that the subject is serving society and his or her own benefit is not the *only* consideration of a therapeutic subject's physician, as would be the case outside the research setting. This suggests perhaps that both therapeutic and nontherapeutic research should offer compensation to those who incur injuries while participating. A minority argument contrary to this point was expressed when it was noted that all medical practice produces benefits from learning. Thus, research medicine is not unique in providing new information.

In continuing the discussion of the kinds of research that should have a compensation mechanism in place, one physician expressed the concern that to draw a line between therapeutic and nontherapeutic research is much more difficult than one might suppose. He suggested that if he had a patient with a duodenal ulcer and, with his permission, tested a drug more powerful than was necessary for his condition, this would be therapeutic research. Yet, if the subject were injured by a drug more powerful than his condition warranted, it would only be fair to compensate him for such an injury. As this stimulating conversation drew to a close, Dr. Ryan, chairman of the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, explained that this Commission had abandoned the use of the terms therapeutic and nontherapeutic in referring to research in general and had adopted in place the term therapeutic *procedure* and nontherapeutic *procedure* for specific treatments or tests. Time restricted further discussion.

Part 5

CLINICAL RESEARCH ON CHILDREN

Robert E. Cooke

There is a unique importance to research on infants and children; yet they represent the group least able to consent, assent, or object meaningfully. Questions, therefore, arise as to the ethical justification for such research. Considerations include: proxy permission in lieu of consent; the concept of the family as a partially autonomous unit requiring respect but also possessing obligations; the question of for whose benefit—child or caretaker—research permission is granted; and the concepts of graded autonomy and graded childhood. Each of these considerations lends some justification to the practice of research with infants and children.

The National Commission for the Protection of Subjects of Biomedical and Behavioral Research has completed and released its report, *Research Involving Children*. Prior to that report it had considered research on the fetus, research involving prisoners, ethical principles underlying research, and psychosurgery. Without question the Commission had more difficulty in arriving at its recommendations in regard to children than in any of the other charges given it by Congress. There seemed to be more areas for difference than in all the previous deliberations. I am personally less satisfied with our conclusions in this case than in our other reports.

S. Hauerwas, in his paper to the Commission on Ethical Issues in the Use of Human Subjects, affirms this belief.

> The ethical issues raised by the use of prisoners and the poor seem simple when compared to the problems involved in the use of children and other non-competents. In order to develop certain kinds of drugs or procedures we can do all the animal and adult testing we want and still we must finally test on children—i.e., a test group who by definition cannot give informed consent. Paul Ramsey has argued that no one, parent or guardian, even with the best intentions has the moral status to consent for a child to be made the subject of medical investigation solely for the accumulation of knowledge (except when epidemic conditions prevail). To quote: "Where there is no possible relation to the child's recovery,

> a child is not to be made a mere object in medical experimentation for the good to come." If it is objected that this severely restricts possible advances in childhood medicine, Ramsey argues that the moral progress of the race is more important than the scientific. Thus, testing of children is the paradigm instance that at times it may be necessary to choose between morality and knowledge even though we normally assume that we do not have to choose between them [1].

Five areas seem to me to be of particular significance.

1. The ethical justification for research involving infants in contrast to others in our society—namely the survival imperative.
2. Proxy permission in lieu of consent.
3. The family as a partially autonomous unit requiring respect and possessing obligations.
4. The question of benefit for whom—child or caretaker.
5. Graded autonomy and graded childhood.

These issues consumed much time and energy and were resolved only partially despite much discussion. The practical significance of the first three, at least, can be appreciated somewhat from the following personal research experience, which dramatizes but does not exaggerate the problems.

Heat Stress on Infants Study

In 1948 two associates and I were concerned with the effects of heat stress on young infants. The reasons for that interest were that a large number of infants live under circumstances in which there is significant heat stress, that evidence from studies in adults might not be applicable to infants, and that there was no information available as to what feeding mixtures were appropriate and what water intakes were proper under such circumstances. We carried out extensive balance studies on a series of infants—4 weeks to 6 months of age—in a controlled environment comparable with hot summer temperatures. Changes in body water and electrolyte that occurred over a number of days were calculated from precise measurements of intake and output, including skin washings, blood chemistries, and body weight. The infants, all black, came from an orphanage in which personal attention was extremely limited because of inadequate financial support. During these studies the infants received far better attention from our round-the-clock "foster mothers" (nurses) than they had in the orphanage. In our minds the improved care compensated for the fact that we had to draw blood from these babies using techniques that were not without pain or risk. These infants were also subjected to the additional discomfort of being restrained for the purpose of

collecting urine and stools for a number of days in an unpleasantly warm environment. At the end of the study the infants did have the great advantage, compared with other infants from that orphanage, of being placed in foster homes.

Retrospectively, my guess is that in the long run those infants were probably not harmed and may actually have had benefits by virtue of their unconsented participation. On the other hand, looking at these experiments from my present perspective and that of existing institutional review boards, or from the standpoint of the Commission's recent report, I would conclude that those experiments could not be done at the present time for many reasons, including discrimination in the selection of subjects. Yet, was the work worthwhile?

The balance studies showed remarkable retention of sodium during heat stress, which produced rather serious intracellular dehydration (despite weight gain) leading to significant illness and fever. As a consequence of those experiments there was a major change in the feeding practices for infants throughout the world, with a substantial decrease in morbidity and mortality everywhere.

Justifying Research With Young Infants

This experience illustrates the particular problem of ethical justification of research with children. The human infant, because of the extreme immaturity of the species at birth, requires many interventions to survive, compared with the adult. What interventions are necessary, when should they be made, how much must be established to prevent serious harm to substantial numbers of normal individuals? The premature infant, for example, is not an abnormal part of our species but a human being in the early stage of life. Such normal individuals will be seriously damaged or die in large numbers unless interventions are appropriate. The central nervous system is immature, as are the respiratory, gastrointestinal, and urogenital systems. Adaptability is so limited that if the interventions are not tuned very finely, there is no survival. We are not talking about having people lead happier and nicer lives, we are talking about survival. That fact introduces into the area of infant and child research a new imperative—not a scientific imperative that we must have more knowledge—but a survival imperative. If interventions are not appropriate, large numbers of individuals die or are seriously damaged.

If oxygen is not administered to immature infants, many deaths occur. If too much is given, blindness results. If chloramphenicol to prevent sepsis is given to prevent babies from dying of infection, the death rate increases from the "gray baby syndrome." A drug such as Gantrisin, which is well-tolerated by adults, produces kernicterus, severe athetosis, and cerebral palsy. Yet the answer is not simply going back to the old way. We know, for example, that for a substantial number of babies in some parts of the world breast milk is inadequate as a feeding mixture and that infants will not develop and thrive.

Thus a serious problem exists in regard to research in infants and young children, who cannot ever give responsible consent. If interventions are inappropriate, there is no benefit; but there also can be very serious harm. Giving too much water to a baby can produce serious damage. Too little water can produce damage also. Those of you as old as I may remember the days when premature infants were not fed for 3 to 4 days so they would not die from aspiration. Cerebral palsy and death were probable consequences of the hypernatric dehydration that some suffered.

How do we ascertain such consequences? Do we rely on trial and error, as with the use of oxygen, where literally thousands of babies were blinded? Or do we carry out research? Do we learn something about normal human development so we can anticipate problems and avoid a rise in infant mortality as a consequence of the use of a drug such as chloramphenicol? I conclude that research in infancy is necessary to prevent widespread harm. In contrast, an absence of research later in life—although depriving us of significant benefits—would not result in a great amount of harm.

The prohibition of research such as described, if proposed to be carried out on normal healthy white infants of upper-class educated parents, would certainly be explained in terms of the limitations of proxy permission or consent.

> No parent has a legal right to give consent for the involvement of his child unless for the benefit of that child [2].

No one has the right to volunteer another for someone else's benefit.

What Is Consent?

If research on infants and children is so necessary, are there ways that it can be ethically justified in the absence of consent by the subject?

To answer that question it is necessary to look at what consent represents. Why is consent important from an ethical perspective? Most people agree now that, even though no risk or harm is involved, except for observational activities in public places consent of someone is necessary if you are doing something with that individual. That means that consent is important for more than the protection of the individual from physical, mental, social, or economic harm. Further, most people agree that consent might provide some protection, but it is clear that such protection is limited. Persons are frequently coerced unknowingly. For example, a patient who has a 100 percent fatal disease cannot easily resist the trial of a new therapeutic measure. He or she is going to die without it—and might live with it. There is obviously not very much freedom of choice in that situation, but there is a great deal of subtle coercion. Even more subtle than that is the physician relationship with the patient. The patient respects the doctor; the patient is somewhat indebted to the doctor.

If one reads consent forms carefully in the cancer chemotherapy area, for example, one would have to be a clinical pharmacologist to understand what is meant. Indeed the institutional review board preliminary report to our Commission indicated that the reading level of most consent forms is about 3d- or 4th-year college level. The comprehensibility was at a very high level, and the comprehensiveness was at a relatively low level. Thus in the consent process, people can give responsible but uninformed consent. Consent is poor protection. Institutional review boards can provide far better protection against physical or mental harm than consent. Yet consent is said to be important for two other reasons: respect for the autonomy of the individual and respect for the dignity of the individual. Even though there is no risk, we expect consent out of respect for the freedom of the individual to choose, and out of respect for the person as an individual.

How then do these aspects of consent apply to the infant or young child?

Consent and Autonomy

Autonomy means freedom to choose—the ability to determine one's own course of life. However, such a concept is meaningless when applied to the infant. Consent to recognize autonomy when autonomy is not present is nonsense.

Consent out of respect for the dignity of something or someone does not have to be given by the individual. For example, we do not allow a cadaver to be mutilated. Before one can do an autopsy, permission from a caring person must be obtained. We have certain respect for dignity also. We do not allow people to desecrate a mountain; we require some acceptance by the community. The consent to recognize dignity does not have to be given by the mountain. The experiments that were rather horrifying to the Commission in which a dead fetus was decapitated and perfused to study brain metabolism lacked respect for the dignity of the fetus, even though people might have agreed to abortion. Decapitation of a fetal dog and perfusion would probably not generate that kind of revulsion. Consent, then, can be given to recognize the dignity of other individuals.

Family Consent

How do we justify carrying out research in the individual when it is not for his benefit? Richard McCormick takes the position that one can make the presumption of what an individual ought to do. Natural law doctrine indicates that individuals owe something to other members of the human species; they have an obligation to assist. If one makes a presumption of what a child would wish, the child would not only wish to do this but ought to do this. Unfortunately, I cannot agree with that approach in its application. If applied, one should be able to draft adults for nonbeneficial research because adults ought

to assist. No one is recommending the drafting of adults as research subjects; therefore, no one should draft infants. That is simple justice.

Hauerwas looks at the problem from a perspective similar to mine. He does not assume what a child ought to do but what a child *is* or *is not*. He agrees with what every pediatric researcher would agree with—namely, that a child is *not* a small adult—morally as well as physiologically. He further asserts that the child must be viewed as an integral part of a family—a "natural" in Aristotelean terms, not a contractual institution of society.

> We do not ask to be born into families, we simply are born into families of one kind or another. In a decisive sense the family is not a voluntary institution and the kind of responsibilities that accrue in it are thus different. Morally children are not simply smaller, younger, dependent, and less "rational" than adults. Morally the meaning of "child" is relative to the interests and needs of the community as mediated through the family.
>
> In other words, to speak of family and child is exactly to speak of duties of parents and children toward one another that are grounded in the concrete expectations of particular communities.
>
> The argument is not one of rights of children but rather one of responsibilities to them irrespective of their ability to make claims upon us. It is not one of personhood. We care for children because they are children, not because they are persons [3].

Trust, love, and care for the child are integral parts of a family. The obtaining of consent by the family for actions toward that child is out of respect for *these bonds*, not out of respect for the child as an autonomous being. Proxy consent can be seen equally as an attempt to protect the integrity of the family unit.

It is true that parents may not always know what is best for their children. The important issue is that the historical tradition of family expects that the family *should*. "In other words proxy consent (or permission) as an institution (or procedure) is one way to insure that whatever is done to the child is done in accordance with the moral conventions and traditions of that family." [3].

My position comes very close to that of Hauerwas. Infants and children are part of families, and of the human race. They are not to be excluded automatically from research because they cannot make decisions on their own behalf—because they cannot give consent. If the family participates in research, if the family heads—the parents—give permission or consent to participate, the younger members can be enrolled, I argue, even though they cannot comprehend or possibly even object.

Permission on behalf of the infant to participate alone is considerably different from consent on the part of the family as a unit to become involved. The family as a unit is recognized by society as having considerable freedom to

choose what is best for itself. What I propose is essentially that research related to members of a family is acceptable providing there is family consent for participation of the family.

What does that mean? It means that the family is enrolled, the parents as well as the child and infant, providing both parents agree; providing the family continues to participate in the studies, that some senior representative of the family is present when there are procedures carried out; and providing they are there as participants to withdraw from the experiments whenever the activities are uncomfortable to the family. Consent of the parents to participate, essentially family consent, recognizes the freedom of families to choose, but it must be a unanimous choice. Thus, in research of a nonbeneficial type both parents must agree; the family must be participants, not simply the infant, and the family is there to withdraw if procedures are painful. The parent can judge and the family and infant can withdraw. This is not proxy consent for another individual; it is consent for family participation.

That kind of consent exists in sociological research. The chief or the senior members of a tribe can consent for the tribe. The heads of organizations/associations can consent for the members, providing you are not harming individual members.

What kind of safeguards do we require if we recognize that the family can provide consent for participation of the family? First, both parents must consent (a one-parent family may not be the most desirable type to enlist). If there is no family, as in the case of orphan babies, research could not be done unless they could benefit immediately, because these individuals are not representative members of a family.

Nontherapeutic research on infants is acceptable under such an approach providing (1) animals, adults, or older children who are consenting, mature minors have been studied previously when feasible; (2) no alternative means are available; (3) the sought-after information is highly valuable to prevent harm and do good; (4) every effort is made to utilize procedures being carried out as part of usual medical and nursing care; (5) the least invasive and the least uncomfortable procedures possible are utilized; (6) the risk is no more than minimal; (7) there is no unfair discrimination in the selection of subjects; and (8) there is careful scrutiny of the motivations of the family that volunteers to participate to ensure thoughtful family consent.

Those familiar with the report of the Commission know that, in general, the Commission did not accept this proposed solution; instead it permitted proxy permission for procedures, approaches, or experiments that did not offer immediate benefit to the individual, providing the risk was only a minor increase above minimal. It suggested but did not require participation of the family and thereby acknowledged the validity of proxy consent or "permission."

The definition of minimal risk was kept so restrictive, however, that it could be considered no additional risk beyond that of everyday living. My objection to the minor increase above minimal rests with the indefiniteness of "minor"

and the likelihood of wide ranges of interpretation of that standard. Admittedly minimal as the limit of risk is vague, but the additional vagary, minor, compounds rather than clarifies the situation.

When interventions are carried out as a part of research that might benefit the child, few physicians, lawyers, or ethicians raise concerns. Permission is granted by the parents or other caretakers with the obvious expectation that all "therapeutic" approaches are directed toward the best interest of the child. Unfortunately, that might not always be the case.

In the application of rules related to the conduct of research or, for that matter, the provision of services, it is important yet difficult to distinguish always between research on behalf of the caretaker and research on behalf of the individual child.

In the study of a group of patients who are hyperactive, are amphetamines given to the child for the benefit of the child, or his teacher, or his parents? Certainly, improved behavior makes life far easier for the teacher and the parents. Yet if the child is appreciated more by his caretakers and his performance is improved, is he not benefited? It is not an easy distinction. A number of years ago in Cleveland carotid-jugular anastomosis was developed to revascularize the brain of children with Down's syndrome so that through retrograde flow there would be a greater volume of blood going to the brain. Was that for the benefit of the parents or for the child? It turned out to be of no benefit, but it certainly was a procedure that could be questioned. Gastrostomy to assist feeding of the severely defective was a common practice in the Sunland Training School in Florida until a short while ago. A tube is inserted, feeding time is shortened, and the budget is reduced in that institution. Such actions were for the benefit of the caretakers, certainly not the child.

As far as therapeutic research is concerned, the child who is not able to consent should not be in the forefront of research. When feasible, where survival of that individual is not at stake, research should be carried out on adults or consenting older children prior to therapeutic research in the younger group. Every effort should also be made to plan therapeutic research to conform as much to the treatment routines as possible, generating as little discomfort and as little risk as possible.

Autonomy From Family

When experimental subjects are beyond infancy and early childhood but are not adults, some responsibility for decision-making may be given to the subjects regarding participation in research, whether classified as therapeutic or nontherapeutic. However, attempts to translate the principle of graded autonomy or graded responsibility for making one's own choices into specifics have not been particularly successful. In principle, if one follows Hauerwas's reasoning regarding the child's place in the family as an element of consent by the family for the child, the degree of emergence of the child from the family

confines is a rough index of the extent of decision-making to be allowed by that child. Participation in school is one mark of such partial emergence from the family, and some assent or dissent could be recognized if given by the schoolboy or schoolgirl. Likewise, independent living outside the family could certainly be recognized as an indicator of the adulthood of the individual. With children between these two limits, approximations must be made based not only on the degree of independence permitted by the family but also on the seriousness and complexity of the problem. Dissent should certainly be recognized if no benefit will accrue—but not if death or serious disability would be the alternative to participation in research aimed to benefit the individual.

Conclusion

I have argued for the unique importance of research especially concerned with young children, even though that is the group least able to consent, assent, or object in a meaningful way. I have argued for participation of the family in recognition of the importance of that unit in society and as a protection for the child's well-being and dignity. The ethical bases for these arguments have been presented only sketchily, and it is hoped they will be developed in years to come as the debate continues.

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CLINICAL RESEARCH WITH CHILDREN

June K. Lloyd

Clinical research is necessary at all ages during childhood so advances in medical knowledge can be made and used to benefit children. The statement of the Medical Research Council of the United Kingdom (1963) provided for research connected with the management of the individual child, and intended for the benefit of that child, to be conducted with the consent of the parents if the child was not old enough to give consent himself. Similar considerations were held to apply to preventive research procedures, such as the development of vaccines. For nontherapeutic research, however, it was considered that children under 12 in the United Kingdom could not give consent to a procedure not of direct benefit and which could carry some risk of harm; furthermore, parents could not legally give their consent to such procedures. Nevertheless nontherapeutic investigations are carried out with parental permission, and virtually all research investigations involving children (therapeutic and nontherapeutic) are submitted to local research ethical committees for approval. The previous opinion of the Medical Research Council regarding the nonlegality of parental consent is being challenged in the medical press but has not been tested in the courts. In many respects, current United Kingdom practice conforms with the U.S. recommendations, but the role of research ethical committees is less clearly defined. There is also no provision for a national advisory committee.

The Rights of Children To Be Involved in Research

The U.S. Commission [1] summarizes the arguments in favor of conducting research in children with two points: the lack of an alternative population, and the consequences of not involving children in research. The rights of children to share in the benefits of advances in medical knowledge and, equally, to be protected from the harmful effects of applying knowledge gained only by studies on animals or adults cannot be overstated. Children are not scaled-down adults in terms of growth or development; neither are they a homogeneous group in terms of their growth rate and the maturation of developmental processes throughout the childhood years. Thus, research is needed across the whole range of childhood. Just as it may be inappropriate to use the results of studies gained in mature adults for planning regimens in children, so knowledge acquired about older children could be inapplicable in the newborn period. Numerous examples can be given of conditions that are unique to the childhood years and have no other mammalian model; these include many of the

congenital malformations and inborn errors of metabolism, as well as some of the behavioral disturbances. Likewise, the physiological and psychological differences between children of different ages, and between children and adults, are becoming better understood, with improvement in such areas as the management of fluid and electrolyte disturbances and drug therapy and with changes in many of our clinical practices, such as the rooming-in of parents with their children in the hospital. The consequences of not involving children in research are far reaching; not only would the development of improvements in treatment for diseases in childhood be restricted, but also the evaluation of new therapies (initially worked out perhaps in animals or adults) would be hampered. Furthermore, research into diseases of adult life that have their origins in childhood would be adversely affected.

To those involved in the care of children, and to those in clinical research in this age group, the needs of children to have research done and their rights in this respect seem so self-evident that it is sometimes assumed that the principles are widely accepted. It could, however, be dangerous to rely on this assumption. Many in our society are concerned about research in children, but not all are conversant with the needs for research or convinced of the rights of children to participate in research procedures. Certainly in the United Kingdom it is necessary to spell out the arguments, as has been done by the U.S. Commission. It is encouraging to note that the first recommendation of the Commission specifically states that "research involving children is important for the health and well being of all children . . . [it] can be conducted in an ethical manner . . . and should be conducted and supported." Such a positive approach is clearly both welcome and necessary.

Therapeutic Research

Therapeutic research on children is designed to hold out hope for benefit of the child involved. The Medical Research Council in the United Kingdom in a review on Responsibility in Investigations on Human Subjects [2] stated that "in the case of procedures directly connected with the management of the condition in the particular individual, the relationship is essentially that between doctor and patient," and it considered that to "obtain the patient's agreement before using a novel procedure is no more than a requirement of good medical practice." In relation to children the statement continued "that it is clearly within the competence of a parent or guardian of a child to give permission for procedures intended to benefit that child when he is not old or intelligent enough to be able himself to give valid consent." I shall return later to discuss views in the United Kingdom regarding the age at which children can be considered to be able to give valid consent, but the implications of this statement would be in general agreement with recommendation 4 of the U.S. Commission. Both countries seem to agree that this type of therapeutic re-

search is necessary and can be conducted, and that it is perfectly valid for parents to give permission on behalf of their children.

It must be accepted that the results of therapeutic research might be, and often are, of greater benefit to future children who have the disease in question than to the individual participating in the research program, but this does not invalidate the principle. In my experience parents will often spontaneously say that they are glad to know that studies in which their child is participating will help other children. Perhaps the most obvious examples of this type of research are the clinical trials of cancer therapy in children. The *Archives of Disease in Childhood* contains a report of the multicenter trial organized by the Medical Research Council of the management of nephroblastoma in childhood comparing two forms of maintenance chemotherapy [3]. Although the group of children assigned to one type of therapy did less well, the survival in both groups was better than had been previously obtained by the uncontrolled therapy of individual patients; no one would seriously question the ethics of this kind of research. It is also important to note that the trial was stopped as soon as results from a different trial in the United States indicated that therapy using a combination of drugs was superior to that using any single drug.

The extent to which parents (and children if they are old enough) should participate in decision-making in therapeutic trials could perhaps be debated. Where two treatment regimens are being compared, how far is it necessary, or even desirable, to burden patients with a discussion of what might be complex technical problems? If their child is receiving treatment that is currently accepted and could be used without question by any medical practitioner, do parents need to know that their child is participating in a trial of this treatment? My own view, which I think would be shared by many colleagues, is that parents should always be fully informed. The recommendations of the U.S. Commission place the responsibility for ascertaining that the research is appropriate, properly conducted, and that parental permission has been obtained on institutional review boards; the U.K. counterpart is the research ethical committee. Current U.K. practice, however, would be that all research programs involving children, whether for therapeutic benefit or not, should be considered by such a committee; and most grant-giving bodies demand a statement that the plan of the investigation has been so approved.

Preventive Research

Research into methods of preventing disease in individuals has tended to be considered as therapeutic research. There are, however, some obvious differences. Children on whom research intended to prevent a disease is carried out are usually healthy at the time of the procedure and might have never contracted that disease; if they suffer as a result of the preventive measure, the problem is of a somewhat different order than that of complications occurring during trials of measures to alleviate a condition from which they are already

suffering. Furthermore much preventive research is actually aimed at protecting the community and children in general. For these reasons I propose to consider briefly this type of research as a separate entity.

The major example of preventive research is probably the development of vaccines for the protection of both individual children and of the community against infections that have their major impact in childhood. Appropriate clinical trials of such vaccines can, in most cases, be carried out only in children, and often only in young children. The Medical Research Council [2] considered that the ethical and legal considerations for trials of preventive measures, such as vaccines, were "the same as those that govern the introduction of a new treatment." On this basis various trials of immunizing procedures have been carried out, the fourth and the latest report of the Medical Research Council's trials of measles vaccines having been published [4]. The results show benefit to the children, who have had a high level of protection lasting now for over 12 years without any untoward complications; there has been benefit also for the community, with a reduction in the incidence of measles. No one has any qualms about this piece of research.

The situation regarding immunizing procedures against pertussis is, however, less happy. The first clinical trial by the Medical Research Council [5] was inconclusive, and further trials were conducted [5,6]. Mass immunization was introduced; but continued doubts about its efficacy, and more recently fears about its safety, have persisted. Even though both retrospective and prospective investigations of the relationship between pertussis vaccination and encephalopathy are still proceeding; the U.K. Government has already agreed [7] that children suffering severe ill effects as a consequence of a public health policy would be eligible for compensation. The Parliamentary Commissioner for Administration has, in fact, criticized the Department of Health for not having sufficiently warned parents about the adverse reactions against the vaccine [8]. The present situation is that the proportion of children immunized fell to 39 percent in 1975, compared with about 80 percent in 1974 [9], and the number of cases of whooping cough in 1977 was 2 to 3 times that in 1976. The Department of Health is now proceeding with a publicity campaign to encourage immunization, but the prospective study regarding the complications of immunization is not complete and may founder because of the low takeup of the procedure.

What would be the ethical constraints of setting up a further trial in this situation? I do not think the Medical Research Council statement gives enough guidance. A disease is not being treated; it is only possibly being prevented, and the risks of the procedure might not be minimal. Nevertheless the problem is an important one for the general health and welfare of children. As far as I understand it, the recommendation of the U.S. Commission that would be appropriate for such a study is number 6, which provides for additional approval by a National Ethical Advisory Board, for public review and comment,

and for subsequent assent by the secretary of the responsible Federal department.

As more emphasis is being placed on prevention I believe that we shall need to consider in more detail how research is to be conducted in this area, and it may be that the coordinating role of the Medical Research Council in the United Kingdom will need to be strengthened by a national body along the lines proposed for the United States.

Nontherapeutic Research

The Medical Research Council [3] stated that for adults nontherapeutic investigations may only be done if "consent is freely given [by the subject] with proper understanding of the nature and consequences of what is proposed," and such consent should be obtained in writing in the presence of another person so evidence is available that a proper explanation has been given, understood, and accepted.

In relation to investigations on children, the Medical Research Council made the following recommendations and, as these remain the main official guide under which research ethical committees operate, I will quote them in full:

> In the strict view of the law parents and guardians of minors cannot give consent on their behalf to any procedures which are of no particular benefit to them and which may carry some risk of harm. Whilst English law does not fix any arbitrary age in this context it may safely be assumed that the Courts will not regard a child of 12 years or under (or 14 years or under for boys in Scotland) as having the capacity to consent to any procedure which may involve him in injury. Above this age the reality of any purported consent which may have been obtained is a question of fact, and as with an adult the evidence would, if necessary, have to show that irrespective of age the person concerned fully understood the implications to himself of the procedures to which he was consenting. Even when true consent has been given by a minor or a mentally subnormal or mentally disordered person, considerations of ethics and prudence still require that, if possible, the assent of parents or guardians or relatives, as the case may be, should be obtained.
>
> Investigations that are of no direct benefit to the individual require, therefore, that his true consent to them shall be explicitly obtained. After adequate explanation, the consent of an adult of sound mind and understanding can be relied upon to be true consent. In the case of children and young persons the question whether purported consent was true consent would in each case

> depend upon facts such as the age, intelligence, situation, and character of the subject, and the nature of the investigation. When the subject is below the age of 17 years, information requiring the performance of any procedure involving his body would need to be obtained incidentally to and without altering the nature of the procedure intended for his individual benefit.

Although this statement does not, as Curran and Beecher [10] have noted, outlaw all clinical investigations on all children where there is no direct benefit to them, it would certainly appear to make investigation on babies or young children virtually impossible. However, the Medical Research Council's advice rested on the opinion of a single lawyer and, although the legal division of the Department of Health and Social Security gave essentially similar advice, the proposals have never been tested in the courts. Many nontherapeutic investigations have been, and are being, conducted on young children in the United Kingdom with parental permission and with the approval of research ethical committees. In most respects the recommendations of the U.S. Commission are already being fulfilled, but there are some important differences.

Function of Research Ethical Committees

Research ethical committees (REC) are the United Kingdom's counterpart of institutional review boards but are not set up or controlled by any central government agency. They were established by hospitals on the recommendation of the Royal College of Physicians of London [11], who outlined the following functions:

1. An REC should be a small committee set up solely to supervise the ethics of clinical research.
2. The medical members should be experienced clinicians with knowledge and experience of clinical research.
3. The REC should have a lay member.
4. To remove any uncertainty about which procedures should be submitted to an REC, all proposed research investigations on human beings should be submitted.
5. Whenever a research investigation is not expected or intended to benefit the individual patient, a full explanation should be given. The patient should be free to decline, participate, or withdraw at any stage.
6. Whenever possible the consent of a patient should be obtained in the presence of a witness.
7. When there are circumstances in which it is genuinely inappropriate to inform a patient fully, the REC should examine the situation with special care.

8. Particular care is needed if a clinical investigation is proposed in children or mentally handicapped adults who cannot give informed consent. The parents or guardians should be consulted.
9. Particular care is needed if a clinical investigation is proposed on a subject or patient who has any sort of dependent relationship to the investigator, e.g., student, laboratory technician, or employee.

Because the Medical Research Council and most other grant-aiding bodies will not give financial assistance unless an investigation is approved by an REC, and because reputable journals will not publish the results of research for which ethical approval has not been obtained, virtually all hospitals and other institutions where research is conducted have REC's. Their composition, however, varies. Except for those in specialized children's hospitals, it is likely that the members have little knowledge of the problems and needs of research investigations with children. Lack of official guidelines as to the conduct of research with children also leads to uneven decisions, and the establishment of more effective ethical committees for consideration of research in children must be a priority in the United Kingdom.

Age of Consent

The age at which a child might be expected to understand a procedure and give or withhold his consent has not been defined. As the exact age is in any case bound to vary from child to child this is probably wise, but the implications of the Medical Research Council's statement are that in England children ages 12 years or under would be regarded by the courts as being incapable of giving consent. This view has never been tested in the courts, and a recent legal opinion [12] has stated that children of any age who can understand and decide about what is involved in a nontherapeutic experimental procedure can legally give consent. The U.S. Commission prefers to use the term assent rather than consent and states that such assent will normally be required for children who are 7 years or older, although parental permission is also needed. Dr. Cooke has cogently argued that the autonomous unit is the family and that, when viewed in this light, the family gives consent. The exact role of the child or parent, therefore, requires less precise definition.

Risk of Procedure

In nontherapeutic research it is assumed that the risk of the procedure must be minimal, or at least small. Risk has not been defined in any U.K. guidelines. The Medical Research Council talks about procedures that "may carry some risk of harm." Value judgments, therefore, have to be made by investigators, ethical committees, and parents. The recent experiences [13] of an investigator

who wished to obtain blood samples from infants have been the subject of a brisk correspondence in the British medical press (*Lancet*). Whereas the U.S. Commission includes obtaining blood specimens as a procedure that would cause minimal risk, the view of an REC in the United Kingdom was that blood sampling for research in infants was not legally permissible. This view was generated in part by the possibility of risk and in part by the fear that the courts would not uphold the parents' right to give permission for such an investigation on their child.

Conclusions

All available evidence indicates that, in general, clinical research in children in the United Kingdom is being conducted according to ethical standards as high as those proposed by the U.S. Commission. However, the relative rigidity and brevity of the only official statements relating to research in children, together with lack of uniformity in the functions of research ethical committees, is undoubtedly hampering the acquisition of knowledge in many areas of nontherapeutic research. Uncertainty about the legality of the consent procedure seems central to the problem. A leading article in *Lancet* [14] sees no way out until a case is brought to the courts for decision; one lawyer believes that nontherapeutic procedures that are in the public interest of a child and are not in any significant way detrimental to the child's interests are perfectly legal [12]. Neither the U.K. Medical Research Council nor the Department of Health has chosen to comment. The U.S. Commission is to be congratulated for having said so much so explicitly.

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DISCUSSION

James B. Sidbury

The U.S. point of view was summarized by Dr. Ryan, who stated that the Commission had attempted to evolve a reference standard for biomedical and behavioral research as guidance for the clinical research committees in the various institutions throughout the United States. The matter of informed consent was of concern to both the U.S. and U.K. representatives. Dr. Cooke's proposal was that the family as a unit be involved in this process, sharing the burden, responsibility, and decision-making.

The U.K. representatives indicated that the standards and design of approval for clinical research resided in the clinical research committees of the individual institutions. Drs. Lawrence, Lloyd, and Weatherall emphasized their belief that each situation should be individualized. They cited the distress of parents asked to consent to participate in a clinical trial of leukemia therapy. Dr. Lloyd expressed a lack of ease with requesting and expecting informed consent on issues that are complex for the trained medical professional with years of experience. Dr. Weatherall cited examples where delay for consent would add risk to the clinical situation.

There was general consensus that good medical practice, particularly clinical research, requires open and thorough communication between the physician, the child, and the family. The concept of involving the family in decision-making was considered a good one. It was unanimously agreed that pediatricians ought to be participants on the clinical research committees when evaluations of clinical research involving infants or children is at issue.

Part 6

ROLE OF THE PUBLIC IN MONITORING RESEARCH WITH HUMAN SUBJECTS

W. E. Waters

The public has a role in monitoring research with human subjects in two distinct areas. The first concerns the selection of particular fields for research programs. These are difficult choices, but with both government money and research charities the public has helped direct research into some fields at the exclusion of others. It is difficult to justify a radical departure from present methods as most important discoveries are made "by chance," although by researchers with trained and open minds. The second role of the public concerns representatives serving on medical ethical committees. Increased representation of lay members on ethical committees is highly desirable.

Few would now confine the responsibility for research with human subjects to the investigators and subjects. In Britain the publication in 1967 of *Human Guinea Pigs* [1] was an explosive and emotional documentation of medical research. It received widespread attention in the daily and weekly press. This chapter will consider the role of the public and its representatives in two aspects of monitoring research with human subjects. The first concerns the general directions of research and the amount of research done in each particular field. The second concerns the scrutiny of individual research projects and, in particular, the nonmedical role in medical ethical committees.

Direction of Research

It is difficult to obtain detailed information on whether the direction of research is in line with what the public wants, but the two are most unlikely to be in even general agreement. How do we measure what medical research the public wants? One suggestion is to examine the contributions to the various research charities, but those who contribute in this way are a small section of society. The public, at least in Britain, is largely unaware of much of the research that is going on and has little or no knowledge of many research fields. However, the public probably would wish to direct research roughly in proportion to the incidence of disabling and fatal diseases in the community, although in practice much research is confined to restricted and apparently "academic"

fields. James Gowans, Secretary of the British Medical Research Council, admitted that the council's research priorities had little in common with the public view of priorities because most research bodies tended to fund "good ideas" that had a likely success of proving a "good" study. Gowan's view, shared I am sure by most in the scientific community, is that the neglected spheres of research are neglected because there are few good ideas for research studies in those areas. In part this is the old conflict between "pure" and "applied" research.

The organization of medical research in Britain, now mainly funded by Government, was much altered by the recommendations of Lord Rothschild in 1971 [2]. Research was divided into "basic research" and "applied R&D," and the concept of the customer-contractor relationship was established with the Department of Health and Social Security acting as "customers" and the research investigators as "contractors." The Government, acting through the political process and presumably on behalf of the public, has had an increasing role in the direction of medical research in Britain. The Department of Health and Social Security has increased its research expenditure in recent years. In 1975-76 it spent £18 million as well as commissioning a further £8 million of biomedical research from the Medical Research Council [3].

However, even this much research money from the Department of Health and Social Security and commissions from the Medical Research Council are not in proportion to the "burden of disease" in the population. Measured by a composite index based on inpatient and outpatient data, general practitioner consultations, morbidity as identified in Social Security information, and mortality statistics, expenditures on respiratory disease are less than indicated by the burden of the disease. Yet expenditures on neoplasms are more than twice and endocrine, nutritional, and metabolic disease more than six times that indicated by the burden of disease in the population [3]. Owen has given information on the changes in the percentage of the Department of Health and Social Security health and personal social services research expenditure between 1972-73 and 1976-77. Mental health increased from 9 to 14 percent, the elderly from 2 to 4 percent, and physical handicap from 1 to 8 percent. Hospital services research declined from 33 to 22 percent of research expenditure over this 5-year period.

Individual Research Projects

There have been a number of statements to guide researchers in clinical research. The Medical Research Council in 1964 issued a report on the responsibility of investigations on human subjects [4], which greatly expanded an earlier memorandum of 1953. The World Medical Assembly adopted the Declaration of Helsinki in Finland in 1964, and this was revised by the 29th World Medical Assembly in Tokyo, Japan, in 1975 [5]. These guidelines, at least in Britain, have no legal backing. The Royal College of Physicians has,

however, recommended the establishment of ethical committees, and these have gradually increased in number over the last 10 years. Again, these ethical committees have no legal standing; probably much medical research in Britain is still not submitted to the secretary of a medical ethical committee. This is not to imply that this is unethical research; many projects not submitted to an ethical committee are trivial, and submission is deemed unnecessary. The influence of these committees is, however, much on the increase. Some grant-giving bodies now require proposals for research funds to come before such committees. There is no doubt in my mind that the ethical committees have been at least partly responsible for a change in medical research that has been apparent in Britain since Papworth's exposé, which began with radio and television programs in 1960 [6] and culminated in 1967 in *Human Guinea Pigs* [1]. This change in research is now apparent to editors of medical journals in the papers they receive for publication.

The public often assumes that physicians are trained to be responsible and need no supervision in research. Yet medical ethics is at best a late entrant into most medical school curriculums, and many medical researchers regard any supervision of their research as restricting their "freedom." The concept of clinical freedom in treating individual patients sometimes seems to carry over into research investigations. Individuals involved in detailed research could lose a sense of perspective. In general, research discoveries of the greatest importance have been to a large extent "chance" events, but it is important to note that the important observations have been made by trained minds. To call the discoveries "accidents" because the results were often not envisaged is perhaps misleading. However, perspective regarding the benefit of research must be kept.

In the United Kingdom there seems to be little uniformity on the composition or methods of working of ethical committees, although the current position is difficult to review. Some ethical committees now contain lay members. I am on the joint ethical subcommittee of the Hampshire Area Health Authority and the faculty of medicine of the University of Southampton. This committee has a lay chairman (who is legally qualified) and a representative from the community health council (who happens to be a nurse). Papworth [6] suggested that it should be compulsory for ethical committees to have a lawyer, a nurse, a theologian, a laboratory or x-ray technician, and a clinician who has never played a prominent role in research. He has strong views on the failings of many ethical committees and states that "very few such committees in Britain have any non-medical representatives." At present little is published on their composition, numbers, or activities; a review of their structure and work is much needed. Newcastle analyzed 249 applications received between April 1972 and August 1976 [7] by a working group comprising a bishop (as chairman), a lay member, a nurse, a retired administrator, and another academic theologian. Eighty-six percent of the applications were given approval on the first consideration, and only one project

was completely refused ethical approval. It is important to consider the main function of these committees, which is to safeguard the interest of patients, volunteers, and the public. They should also help to protect the reputation of the investigators and the research institution or hospital, and to carry conviction and to reassure the public it is right that they have a reasonable lay representation.

Lay representation can be particularly important in helping to identify some of the difficult ethical problems of medical research, including informed consent and the manner in which it is obtained. Some disquieting facts about lack of information to patients have been reported by Gray [8].

The various research guidelines, such as the Statement by the Medical Research Council [4] and the Declaration of Helsinki [5], place stress on informed consent, but I believe it is sometimes not reasonable, or even ethical, to discuss in great detail with an ill patient all the possible implications. Whenever a doctor treats a patient he or she does not always discuss all the possibilities that might happen. Obviously there are occasions when the patient should be informed of various risks, but not with every penicillin injection or aspirin tablet. Similarly, in medical research, in a randomized clinical trial of, say, two treatments, I doubt if the complete catalog of possible adverse effects of both treatments should always be fully described. Nonmedical representatives on ethical committees can be of great help in discussing with researchers how the study should be explained to patients.

Further, they can help in deciding if all individuals in clinical trials should know that they are in such a trial at all and, if so, how they should give consent. The guidelines would suggest that they always should know, but this would mean one could never do clinical trials on unconscious patients. It would also severely restrict trials on the very ill. Do we want this? For example, there may be instances where the patient, at the height of the illness, would worry unduly about having the full details of a clinical trial explained. Imagine a clinical trial between early or later gastroscopy in cases of suspected bleeding from the stomach. Some might be of the opinion that in such examples clinical trials can never be done. However, it must be remembered that many accepted medical treatments become established with little scientific evidence, and if there is genuine doubt about treatments it may sometimes be as unethical not to do research as to do research. Claude Bernard noted, "So, among the experiments that may be tried on man, those that can only harm are forbidden; those that are innocent are permissible; and those that may do good are obligatory." [9].

However, it is not always, or even usually, easy to classify individual research projects into these three groups. The randomized clinical trial is an important tool in research, as Cochrane has so clearly shown [10]. It does have important, and often difficult, ethical problems [5], and I believe that these are best discussed with lay members on ethical committees as well as by researchers and medical practitioners with no particular involvement in research.

Ultimately we might have mainly lay committees with access to medical specialists for facts and expert assessments of risks and benefits. It is important for progress that the general public have confidence in the conduct of medical research. Lack of trust will redu[illegible]e willingness of the public to help in research, and in many projects a high[illegible]sponse rate is desirable. In the future it might be helpful if the various research guidelines were more specific for different categories of research; for example, patients; controls (who may also be patients or healthy volunteers); studies that use or link patients' records or other personal data; and epidemiological surveys of the general population. Also the guidelines should more clearly distinguish between research procedures from which the subject was unlikely to benefit and research procedures where all patients might benefit.

In 1964 the *British Medical Journal* [9], discussing research ethics, said that "the medical profession has departed far enough from elementary principles of human behaviour . . . to show that pious general statements are of little, if any, value." Research depends on the trust of the public. Ethics must be clearly distinguished from legal considerations and from professional etiquette. Lay members of ethical committees may be particularly good at helping to make that distinction. In an increasingly questioning world, the public, through its representatives, has an important role in monitoring research with human subjects.

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ROLE OF THE PUBLIC IN MONITORING RESEARCH WITH HUMAN SUBJECTS

Michael P. Hamilton

This chapter discusses the current role of the public in medical policymaking, citing growing citizen interest in the uses of scientific and technological advances to promote economic justice, world peace, and a sound ecology. Some comparisons are made between British and American attitudes toward medical experimentation. The history of institutional review boards in America and lay representation on them is outlined, particularly in relation to emerging policies at NIH. In terms of personal experience, the chapter outlines the role of a community representative on review boards, inadequacies in consent forms, and the differing interests of the chief parties to human experimentation. Discussed finally are four unresolved problems: the limitation of financial resources for medical research funding, the immorality of transferring research to countries where ethical standards are relatively low, the selection of community representatives on institutional review boards, and the issue of compensation for injury incurred in research. The chapter concludes optimistically, noting that with a free flow of dialog between the medical community and the public, appropriate and creative compromises can be made in conflicts.

Our times are characterized by scientific and technological advances in practically every sphere of domestic, national, and international life. In the United States the times are also characterized, and this is partly in response to these new issues, by a resurgence of citizen interest and involvement in public policy decisions and in the consumerism movement. These movements focus on the proper use of new technological powers and artifacts, for what purposes and by whom, their effect on human society and the ecology of nature, and finally the funding of continuing research.

The field of medical practice and research is no exception to this activist phenomenon. It is illustrated by the public debate on such matters as the care of the dying and the Karen Quinlan case, the merits of abortion and recombinant DNA research, and the ethics of human experimentation, with particular interest in the occasional abuses. Three abuses stand out: the Tuskegee Study, where 400 syphilitic black men were kept on an arsenic and mercury treatment versus placebo long after penicillin was discovered; the use of retarded children at Willowbrook (N.Y.) Institute to test the efficacy of gamma globulin to provide immunity to a hepatitis virus and the filling of vacancies in Willowbrook with only those children whose parents were willing to consent to

their entering this hepatitis study; and the experiment by a Sloan-Kettering Cancer Research Institute investigator in which live cancer cells were injected into elderly, chronically ill patients without their knowledge.

By and large the vast majority of decisions regarding medical practice and research are still made within the medical professions; but when a new and controversial policy question arises, the implicit constitutional role of the citizenry becomes explicit. For us to discuss today whether the public should be involved in medical policy would be futile. Americans want to be involved, both on the public policy level as well as the local and sometimes individual patient level. Our task is to explore how such involvement can be most creatively and responsibly exercised. Although this phenomenon of public involvement is typically American in character, other nations, including Britain, have undergone similar evolutions and have sometimes taken leadership. However, the United States Department of Health, Education, and Welfare's guidelines for federally funded human experimentation go beyond others in their extensiveness, and the surveillance and control of research funds by Congress and governmental agencies is relatively close.

The difference between our country and the current situation in the United Kingdom was brought home to me quite vividly in a recent conversation I had with a British doctor who had just arrived in the United States. He was amazed at the lack of public trust in the competence and integrity of medical researchers in the United States, as evidenced by the HEW requirements for consent forms. He thought these regulations an example of unwarranted interference. I thought his attitude was out-of-date paternalism. Our conversation continued in a private and spirited letter-writing debate. He wrote:

> You spoke of the necessity for ethical review and informed consent, citing as justification past and horrific violations of individuals not able to protect themselves. Is it honestly thought that such deeds would be perpetrated again if the presently very restrictive attitudes were relaxed?

I replied:

> Yes, I honestly think horrific violations of medical ethics will continue to occur in spite of past experience and new guidelines. History would seem to be on my side . . . .

His hurt feelings at my lack of confidence in medical good will were matched by my surprise at his optimistic view of human nature. Our personal exchange mirrored what has occurred in the last two decades on the larger scene, where the medical profession in the United States has been subjected to more restraints than in the United Kingdom. Whether this difference reflects a greater propensity to unethical behavior among American doctors as compared with

British or whether it reflects a superior sensitivity to moral issues among Americans, resulting in controls to limit unethical behavior, is a matter I would prefer you to argue about rather than venture a personal opinion.

In this chapter I will outline the history of the review process of human experimentation in the United States, offer some personal opinions on the nature of consent forms, discuss the dynamics between the chief parties in medical research, and mention some hitherto unresolved issues.

Background

To understand how this phenomenon of citizen involvement has come to pass, we must step back a little and examine the development of policy review boards and the presence of lay representatives within them. For much of what follows of a historical nature, I am indebted to articles by Robert M. Veatch [1] on human experimentation committees and by Mark S. Frankel [2] on the development of guidelines for these committees.

Nineteenth century medical researchers could do much as they liked, following only their own consciences and whatever interpretation they might give to the Hippocratic Oath. However, the genesis of some kind of informal peer review was recommended by Thomas Percival:

> In the accomplishment of the salutary purpose (of research), the gentlemen of the faculty should be scrupulously and conscientiously governed by sound reason, just analogy, or well authenticated facts. And no such trial should be instituted without a previous consultation of the physicians or surgeons according to the nature of the case [3].

In this century the Nuremburg Code, the Declaration of Helsinki, and the World Medical Association's International Code of Ethics have developed the recommendations further by speaking of the importance of verbal patient or parent consent and the need for high medical standards in research. The conduct of medical research by investigators has, of course, always been indirectly regulated by the fact that editorial boards of medical journals exercise their own ethical standards in relation to the research findings that they choose to publish.

In 1953 when the National Institutes of Health Clinical Center opened, a guideline entitled Group Consideration of Clinical Research Procedures Deviating From Accepted Medical Practice or Involving Unusual Hazard, published in the same year by the U.S. Government Printing Office, stipulated for the first time that the written consent of the patient was to be gained in cases of hazardous experimentation. This administrative procedure required documentation of what went on in the hitherto sacrosanct privacy of the doctor-patient relationship.

In 1962 Congress passed the Drug Amendments Act, authorizing the Secretary of HEW to regulate the testing of new drugs and requiring that the consent of subjects involved in these tests be gained [4]. In December 1965 the National Advisory Health Council proposed the establishment of institutional review committees for clinical research and investigation involving human beings. Three purposes were given: the protection of the rights and welfare of the individuals involved; the appropriateness of the methods used to secure informed consent; and the risks and benefits potentially involved in the experiments. The following year, these recommendations were made requirements for grantee institutions by action of the U.S. Surgeon General.

The composition of such review committees was not fully spelled out, but an interdisciplinary group was implied. James A. Shannon, Director of the NIH from 1965-68, had already been thinking along these lines and indicated that representatives from the society at large who had ethical, moral, or legal interests should be involved with medical professionals in the establishment of guidelines for human research [5].

Parallel to these developments has been the emergence of local hospital committees with community representation addressing themselves to a variety of nonresearch type medical dilemmas, such as the selection of patients for dialysis treatment when there are insufficient machines to go around, the selection of patients for transplants, and more recently, advisory committees on the care of terminal patients.

For those interested in the constitutional and legal elements of review boards, there is a draft report available [6]. This report also treats a number of questions still unresolved about the functioning of review boards. In addition there is a report, largely a statistical analysis, on the performance of institutional review boards that was made to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [7].

The current requirements for lay representation on institutional review boards for HEW-funded grants and contracts supporting research when human subjects are involved are (quotations only relevant to lay participation follow):

> **46 106**
>
> (b) (1) . . . In addition to possessing the professional competence necessary to review specific activities, the Board must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable law, standards of professional conduct in practice, and community attitudes. The Board must therefore include persons whose concerns are in these areas.
>
> (4) No Board shall consist entirely of persons who are officers, employees, or agents of, or are otherwise associated with the institution, apart from their membership on the Board.

(5) No Board shall consist entirely of members of a single professional group [8].

Finally, there have been some developments on the national scene in America wherein important committees with lay representatives have greatly influenced the recent practice of human experimentation. First was the establishment by Congress in July 1974 of a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. With a large staff and the cooperation of many consultants, it has produced some excellent and wide-ranging recommendations. A permanent National Council for the Protection of Human Subjects is intended to replace this Commission when its mandate ends. HEW Secretary Joseph Califano set up an Ethical Advisory Board in 1977 to provide policy advice on current medical issues. Since this board plans to meet only every 3 months and has a relatively small staff to support it, their ability to provide new and creative insights is yet to be shown. Finally, Senator Edward Kennedy is reported to be trying to persuade the White House to organize a Presidential Commission for the Protection of Human Subjects to deal with medical issues that arise in the private sector, or in government research outside the jurisdiction of the Department of Health, Education, and Welfare.

The Role of a Community Representative—Personal Experiences

As previously mentioned, HEW regulations call for community representation in Government-funded human research review boards. The kind of people frequently invited include clergymen of one denomination or another, social workers involved in community health programs, or lawyers interested in consumerism and patient rights. Why one person or kind of person is invited and another not seems to be a haphazard process. I was known to some local NIH physicians as somebody interested in medical issues, so in 1972 I was invited to join the policy board overseeing the clinical trials of Trial Use of Hyper-Immune Gamma Globulin for the Treatment of Hepatitis, funded by the National Heart and Lung Institute of NIH. In 1975 I became a member, for approximately 18 months, of the medical board at the Clinical Center at NIH. This was later named the Volunteer Research Panel and is now defunct. In 1976 I joined the policy board of the Persantine-Aspirin Reinfarction Study, which was a double-blind, randomized clinical trial funded by a German drug company. Finally, in 1977 I became a member of the Clinical Research Subpanel of the National Institute of Allergy and Infectious Diseases at NIH.

I wish I had kept a record of all the interventions I had made in the discussions on the various boards of which I was a member. I must have been involved in the review of perhaps 200 protocols and probably asked for changes in the consent forms in about one-third of them. In addition I asked

questions relating to the form's design or for clarification of technical procedures and expressed doubts about the overall merit in about 5 percent of them. In about 5 percent of the protocols under review I tried to draw some general policy conclusions from what we had learned in a discussion. Around the table with me on these boards were doctors with national reputations for excellence in their field, statisticians, biologists, chemists, Ph. D.'s in esoteric fields, supervisors of nurses, and occasionally another lay representative. Frankly, it was an intimidating environment for an outsider to enter, and at first I felt like a rude, crude lion in a den of talented, sophisticated Daniels! I decided that if I were to be of any use, I would have to be honest about my feelings and questions, not be overawed by expertise, and, as far as my Irish temperament permitted, speak in a restrained and rational manner.

How well I and other lay representatives have served these boards is not for me to judge. I will say that I have been very favorably impressed and grateful for the nearly total support which was given not only to me personally, but to the recommendations I have made. I cannot recall a single instance in which I requested a change based on ethical values that, once understood, was not accepted. Sometimes the vote was close, sometimes the argumentation was painful; but mutual respect was never lost.

Most laymen's involvement in review boards focuses on the consent form since it is the chief document of the interface between the doctor and the patient. Some doctors consider consent forms cumbersome, frightening, and—because few patients understand them—of little value. I agree some are cumbersome—they deserve to be better written. I agree some are frightening—but shall we bypass the knowledgeable cooperation of the patient by not identifying the risks and discomforts involved? I agree that some patients will not understand them—but the very process of composing a good form helps the doctor be sensitive to what is happening to the patient as a human being. This last point of the effect on the doctor is one I would like to emphasize.

However, the composition of consent forms is only half the task; how well the actual explaining of that form to the patient and the gaining of his or her consent are done is equally important. Frankly, I have not yet had the time to do such followup work, and I suspect few other community representatives have or will. It seemed wise to address myself first to the task at hand of getting investigators accustomed to writing good forms. It is an area for further research.

The elements required in consent forms for Government-funded research are set forth on page 3 of *Protection of Human Subjects* [8]. I would like to see two additions: a requirement that payment or other reward for participation in the research be included, and some statement about the degree of confidentiality of data collected. Both of these elements are required in NIH intramural research.

Inadequacies in Consent Forms

As a layman I found I was more aware of certain kinds of inadequacies in consent forms than medical professionals.

Technical Language

Each profession has its own jargon. Doctors tend to forget that the patient does not necessarily understand medical terminology, even when it is in frequent use in medical groups.

Inadequate Information Regarding Pain

The following description omits reference to muscular pain:

> Liver biopsy using a hollow needle is a commonly used technique for obtaining liver tissue to analyze under the microscope. The skin over the right side of the lower chest is cleaned. The site of insertion of the needle is numbed with local anesthetic and a small cut made in the skin. You will be asked to hold your breath while the needle is quickly inserted into the liver and removed bringing a core of tissue within the needle. You will then be asked to lie on your right side for 2 hours and remain in bed for an additional 12-24 hours.

Exculpation

Some investigators, perhaps due to hospital or institutional pressure, include in the consent form a statement wherein legal liability of the institution is reduced. Apart from the fact that this is not legally possible, it places undue anxiety upon the patient. An example is:

> I hereby assume all risks, hazards, and side effects associated with or which may derive from such a procedure except where such risks or hazards are the result of negligence . . . .

Hide the Placebo

In clinical trials where, let us say, two different dosages of a new drug are being administered along with a placebo given to a control group, it is possible by use of technical language to hide from the volunteer the fact that a placebo will be used at all. Hence the patient, who may be seriously ill and desperately hoping for relief from the new drug, enters the trial with the false expectation that he is bound to receive it.

Catch-22

A phrase in the consent form is sometimes included to this effect:

> I fully understand the above information, appreciate the risks and benefits involved, and I freely consent . . . .

If the patient does not understand the content of the consent form, he or she probably does not know that fact and, therefore, should not ever be asked to say he or she does.

The Everyday Life Fallacy

> I further understand that there are no greater risks involved in these tests than my infant is exposed to in daily living.

The dangers to which infants, or others, are exposed to daily vary greatly between Harlem, Chad, Belfast, and Grosse Point, Michigan. A more precise definition of risk involved should be required.

Interpretation of Terms

In the consent form of a recent research protocol the phrase "unlikely to occur" was included. I conducted a poll of 16 doctors and other medical personnel present in the room to learn what "unlikely" meant to each of them. Their answers resulted in a range of incidence from 1 in 10 to 1 in 1 million! In the same consent form, the following terms were used with the following interpretations:

"possible"	from 1 in 10 to 1 in 500,000
"rare"	from 1 in 100 to 1 in 1 million
"very rare"	from 1 in 1,000 to 1 in 5 million
"extremely rare"	from 1 in 10,000 to 1 in 10 million

These results suggest to me that numerical incidence is a better way of communicating risk than words.

I believe the quality of consent forms is improving as investigators become experienced in composing them. My own view is that they are just as important as any other procedure described in the research protocol and that their excellence should be mandatory.

Doctor, Patient, and Lay Perspectives

From my experience in serving on review boards, I would like to offer some observations regarding the differing interests of the chief parties to human experimentation.

The Medical Researcher

The medical investigator is usually highly motivated to find a new means of treating or understanding of an illness, and to gain this information as quickly as possible. He or she wishes that the work will enhance professional status and hopes to be able to publish the research findings before any peers. In addition, the researcher is concerned for the welfare of the individual enrolled in the experiment. The ranking of importance of these motivations will vary from one doctor to another and from one experiment to another. If these are the true motivations, they explain why the doctor tries to enroll patients as quickly as possible into the experiment and tends, sometimes unconsciously, to play down the danger or discomforts visited on those patients. They also explain why researchers believe their efforts are worthwhile and why they do not appreciate being distracted by time-consuming review procedures or any regulations that seem to impede their work.

Most medical researchers are very busy people; their education is specialized and intense. Doctors spend most of their working lives talking about medicine. Their brilliance and professional prominence has been hard earned by long hours of work, but it often results in ignorance of current political realities and changes in social values.

The Patient

The patient's concern is usually to be cured as quickly as possible with as little financial cost as possible. Thus, when in a drug trial, each participant would prefer to be the recipient of the new drug being tested rather than receiving the normal treatment or placebo. In addition, one might desire to offer oneself and one's body as a source of information to help the treatment of others in years to come. As long as an unduly large reward for participation is not offered, altruism and freedom of choice can be presumed.

Patients are in a highly dependent state. They are sick and rely on the doctor as the means to health. Although one might fear experimentation, the disapproval of the physician probably is even more frightening.

John Fletcher, the clergyman mentioned earlier as working at the NIH Clinical Center, observed this phenomenon:

> It is well known that ill and hospitalized persons show a marked tendency to be dependent. Several studies show that the process of hospitalization itself greatly increases anxiety; hence if consent is requested during this period inherent restrictions on choice in the patient may be present. Patients who are being treated in an institution where research is also being done are apt to relate requests to do research to their own expectations about treatment. The patient might feel an inner reluctance to disappoint a doctor, even

one other than his attending physician, fearing that interest might be lost in "his case" [9].

The Lay Person

The role of laymen in the review of research programs is that of representatives of the community. They are likely to share in the wish to further medical research, but they are free from the doctor's status needs, free from the need to maintain friendships with medical associates, and free from the fear of speaking their mind lest it endanger employment. Finally, laymen are free from the patient's fear of sickness and the dependency on a physician.

Lay representatives, particularly ethicists, can fall into a number of traps. One reaction is that of intimidation, reluctance to voice opinions or ask questions, in a group where the person is outnumbered by professionals who speak a technical and almost foreign language. Another is to respond with arrogance, believing oneself the only valid interpreter of community opinion and moral righteousness. Education in ethics and morality does not automatically provide the "right" answers; it only imparts a sensitivity to ethical issues and some knowledge of how ethics has been practiced. Everybody on the review board shares in the moral responsibility, and everyone should contribute ethical judgments to the general discussion.

An equally dangerous trap regarding moral decisions occurs when doctors abdicate their moral responsibility if an ethicist is present. "Since our ethicist thinks it's right, then we can go ahead!" is a joking allusion to this process that I have heard. Because no person has a corner on the truth, I believe it is essential that everyone on a review board become involved in moral decisions.

Finally, the lay person or ethicist might be uninformed about national affairs and public moods and, in addition, might not grasp the purpose and design of the research nor detect the moral issues hidden within it. This type of person often turns into a nitpicker who demands that an inordinate amount of time be spent changing protocol minutiae but never recognizes the larger faults. The care and feeding of lay representatives by the medical board is essential if they are to be able to make their best contribution. Often they need assistance to identify the moral questions hidden within technical language.

Some Unresolved Problems

Limitation of Financial Resources

Doctors tend to assume that no cost should be spared to save a life and no research be left undone if it is well designed. However, it has become politically apparent that our supply of health dollars is not limitless; as a Nation we have some very difficult choices ahead. How much money should we spend on research when the standard of public health remains so low in many of our

rural and urban communities? Can we really provide dialysis treatment to everybody who wants it? When should the demands for public money for national security or natural ecology take precedence over medical research and health needs?

On these matters it is quite clear that the decisions require the involvement of more expertise than doctors alone have, or members from any other one discipline, for that matter. But doctors ought to be thinking about these matters and preparing their recommendations for public discussion. I suspect the British are further advanced than we in thinking through this matter.

Transferring Research

If a nation considers some experiment unethical in design, it is immoral to conduct that research somewhere else where those ethical standards do not obtain. To argue that such research is acceptable if the other nation's Government does not object is taking advantage of that nation's lack of standards which the investigator or funder's society has already posited as required.

It is also immoral to do research in a foreign country on a new diagnostic method for a disease if a known cure is not also made available to the patients involved. It is immoral to test a new drug that, if found effective, is not then still made available to the patient participants after the research is completed.

Difficult questions arise when useful research findings have been gained in a country with relatively "low" ethical standards. Should they be used by doctors in other countries? Should these findings be published in medical journals, thus giving the investigator prestige and perhaps encouragement to continue? The answer to these questions should be no. The long-term resolution of these dilemmas is best assured by the continual revision of ethical requirements in the light of new experimental possibilities and their enforcement through internationally agreed-on regulations on research.

Selection of Community Representatives

The choice of which lay representatives to place on review boards is not an easy one to make. To do justice to our pluralistic American culture would require hundreds of people on every board. Since that obviously is not a practical solution, how should one go about selection of membership? My observation is that practically anyone can be of help as long as he or she is not medically trained or part of some medical institution. Once so employed, one begins to adopt the values of that profession, to follow their mores, acquiesce in their pecking order, think of patients as meeting hospital and doctor's needs, and speak medicalese.

If clergy are to be invited, it would be wise to draw on the different denominations in turn. Except for the well-known differences between the churches on such matters as abortion, I do not believe it matters much which

denomination one calls on. The personal ability of the representative and his or her knowledge of current affairs is more important than his or her religious or vocational background. One needs an analytic rather than a scholarly mind, common sense more than passion.

Compensation for Injury or Death Incurred in Research

There is a growing public and professional realization that compensation should be provided to those who are injured or die as a result of involvement in human experimentation. I am referring to injury not incurred by negligence and in excess of the natural ravages of the patient's illness. In January 1977, the HEW Secretary's Task Force on the Compensation of Injured Research Subjects made strong and practical recommendations on how this might be achieved. Those recommendations have not yet been implemented. In the meantime, what do we do when, for instance, there is a known risk of Guillain-Barre syndrome occurring in killed flu vaccine research? The following exchange between a flu vaccine investigator and a lay representative on a review board poses the problem in pithy and dramatic form:

Layman:	What provisions for long-term medical care and compensation are made for volunteers who acquire permanent injury as a result of participation in your research?
Investigator:	We have no policy.
Layman:	What happens if a parent or guardian of a healthy child you wish to enroll asks you about compensation?
Investigator:	(pause) We do not enroll them in the program.
Layman:	In other words, you're taking advantage of the lack of intelligence of parents who don't ask this question? It seems that in an experiment where there is a known risk of serious injury and where the knowledge of this risk would be likely to affect the decision of the participant whether or not to participate, information regarding the lack of compensation should be part of the consent form.

As a result of this exchange, the National Institute of Allergy and Infectious Diseases Clinical Research Subpanel requested, after considerable debate, that the flu vaccine protocol involved include the following statement in its consent form.

> There is no present legal provision for compensation for permanent injury that may be incurred as a result of participation in this

study. One possible mechanism for compensation is through litigation in a court of law.

This inclusion caused a storm of protest from the California university involved for a variety of understandable reasons. At a subsequent meeting of the research subpanel a motion was made to rescind this requested inclusion. A lot hung on the disposition of this motion, and it was defeated by a vote of six to five.

The five votes represented the opinion of those who believed that the research was so important that it should proceed without the consent form information regarding compensation, which hindered recruitment and encouraged litigation. It was argued that to include this information was to make these particular research doctors suffer, while others who exposed humans to risk did not. Finally, it was wrong to begin a general policy of compensation by way of an individual research project.

I argued with the majority that the ethical issue had come to clear focus in this particular piece of research, and for the sake of volunteer participants, it had to be met. In addition, the six voters said that new general policies sometimes emerge because of problems arising in individual projects. Finally, we pointed out that we were not mandating compensation, but only providing information necessary for the informed consent of participants, as required by existing HEW guidelines.

I believe that implicit in this debate was an overriding emphasis on one side in favor of the doctors' needs and the importance of research goals. On the other side there was a primary concern for the welfare of the participants. Although a large number of people, including doctors, administrators, and lay representatives, had been involved for years in various committees to explore and promote a general policy for government compensation, I believe the presence of lay representatives among them was crucial to their deliberations. Without such representatives continuing to move the whole compensation matter through the medical bureaucracy I doubt if it ever will come to pass.

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DISCUSSION

Charles R. McCarthy

All participants agreed that advisory committees should review and evaluate proposed research. Furthermore, there was general agreement that such committees should include persons who are not professionals in the medical field. The question of whether the nonmedical participants should be called "lay members," "public members," or "community representatives" provoked considerable discussion. The most important feature of their role according to the discussants should be that they are not professionals and therefore bring a nonscientific perspective to consideration of consent forms and proposed research.

No general consensus emerged on the point, but several participants urged that the nonmedical participants should have a responsibility to alert or educate the public or the local community concerning the protection of human subjects involved in research.

It was noted that the added number of malpractice disputes and litigation in both the United Kingdom and the United States have created a climate of increased suspicion and fear. Research, like other health activities, is affected by this climate. The use of lay members on review panels tends to dampen the fear and suspicion and is, therefore, very important. Furthermore, lay members tend to make their influence felt without creating an adversarial environment that may be inimical to sound research.

Discussion turned to the question of whether it is proper for one country to impose its standards for ethical research on another. There seemed to be general agreement that an absolute relativity in ethical standards is indefensible. It could justify ignoring Nazi atrocities on the grounds that one country must not interfere with the standards of conduct set by another. Similarly, there seemed to be agreement that each country should be faithful to its own standards—even when funding research in a foreign country. Finally, international agreements should set at least minimal standards for all countries that sponsor research. Scholarly journals could do much to ensure that reasonable standards are met by refusing to publish reports of research that failed to meet international standards.

One commentator pointed out that, by improving standards in research, we may be creating new problems in the practice of medicine. For example, the University Group Diabetes Program report was critical of the use of oral drugs for the control of diabetes. Some physicians accept the evidence and have discontinued use of the drug. Some reject the evidence and continue to prescribe the drug. The majority wish to see further randomized clinical trials. But such trials are not ethical because it is unethical to ask someone to enter a

new trial in which the risks appear to outweigh the benefits. Hence we may never be able to obtain the desired information. The gap between standards for research and standards for service appears to be widening. Research is carefully regulated; the practice of medicine is an uncontrolled and unregulated process. Therefore, tightening the ethical controls over research may have a negative impact on health care delivery.

Some discussion of evaluation of review committees took place. At least three such evaluations have been published; they are referenced in Canon Hamilton's chapter.

Questions were raised about the appropriate degree of public participation in research decision-making and resource allocation. All agreed that the public should have some voice, but no one seemed to be sure how much of a voice, or through what mechanisms that voice should be audible.

Finally the point was made that a serious effort to educate all members of ethics advisory committees–particularly the lay members–concerning their duties and responsibilities should be made. Committee members cannot be expected to function well unless they are trained. At the present time little formal training is available.

Part 7
RELATIONSHIP BETWEEN GOVERNMENT AND INDUSTRY IN CLINICAL TRIALS

Louis Lasagna

In a sense it would be admirable for Government and industry to be partners in the search for new medicines, but there is inevitably an adversary relationship between these two sectors of society. Industry is the suppliant, Government the grantor (or rejector) of such boons as the right to market or to be reimbursed for drug purchases under a Federal or local health scheme.

Given these facts, how can one best contrive the rules of the game? It is generally in the interest of the regulated to have requirements spelled out, so at the least complaints can be lodged against a willful and peremptory flouting of the rules by Government. But such spelling out is not without its own dangers.

In the United States, Federal authorities have decreed as a regulatory fiat (not delineated in the relevant empowering legislation) that at least two satisfactory controlled clinical trials are required to allow approval of a new drug. In the past, this has usually meant two *U.S.* trials, regardless of the number or adequacy of foreign trials with the drug in question. Although this requirement is changing on paper to include foreign data, it is not clear to what extent the Food and Drug Administration is willing to approve new entities *solely* on the basis of foreign trials.

Why such chauvinism? It surely cannot be foreign incompetence in performing proper trials. Great Britain has led the way in such clinical experiments, and knowledge about the conduct of such trials is hardly restricted to any one land. Many countries have investigators who are performing exemplary experiments in man.

Access to Raw Data

The reason seems in large part to entail a matter of access to raw data. The FDA does not trust either industry or clinical investigators and points to past examples of fraud or error. But the United Kingdom has taken a different point of view, tending to trust physicians and drug firms. Whether this confidence is misplaced or not can be argued, but I believe that there is a real difference between the two countries in this regard.

The U.K. position is, of course, similar to that which has governed the scientific literature ever since there was such a literature. Published papers do not provide raw data sheets; and it is generally accepted by both readers and editors that authors know how to add, subtract, and divide, perform statistical tests accurately, etc. We know that in fact *this* confidence is at times misplaced, but by and large science and the public have been well served by the assumption that scientists are honest and competent unless proved otherwise.

I believe that the main bulwark against error in the past, as well as now, lies in independent replication of new facts. When a drug has been found effective and reasonably safe in different countries or in different hospitals or by different doctors in the same country, the likelihood of error becomes vanishingly small. Complicity on an international scale is much less likely than honest agreement on incontrovertible facts.

It does seem reasonable to ask for what I have called "naturalistic" experience in a country prior to registration of a drug. Genetic, geographic, nutritional, and other differences may indeed alter the responses of patients to a drug. But cannot such differences be as well (or better) explored from the application of the drug in ordinary medical practice as in another set of controlled trials?

Other Generic Problems

Regardless of the nature of a country's regulations and rules, there are generic problems that can arise from other factors. One is the quality of professional scrutiny. Even a system that uses outside advisers a great deal will have to rely heavily on the competence and attitudes of the professional bureaucrats in the agency. Obstructionism, paranoia, and downright stupidity cannot be legislated out of existence. Nor are these qualities any easier to detect and expose if the system of drug review is more or less hidden from the eyes of the interested public.

The experts consulted also pose problems. In the United States, so-called "conflict of interest" regulations have at times caused committees to be constituted that are far from scientifically or ideologically optimal to deal with the issues. Then there is the phenomenon of the busy expert who barely reads a few documents on the train or plane trip to the meeting and whose vote could be less than informed and more dependent than is desirable on the testimony of the secretariat or expert witnesses.

Ethical and legal problems will become increasingly important in the years ahead. I do not refer solely to the increasingly litigious nature of our society. I refer rather to the dilemma with which we will be faced because of our very success in coming up with new drugs. Placebo-controlled trials are not only ethically defensible, but mandatory. But can one demand such trials when effective (if imperfect) remedies are at hand? Hardly, at least as far as the

welfare of the patients in the trials is involved. However, the patients of *future* generations may, of course, gain by such trials.

What Are We To Do?

Trials comparing the new drug with a standard drug are satisfactory if dose-response relationships can be shown, or if the new drug is *superior* to the old. Failure simply to show a difference between old and new proves very little, since such an outcome can hide all sorts of problems, including the use of a population unable to discriminate between a good drug and a poor one.

I referred earlier to the possibly deleterious effects of rigid rules. One can imagine situations where the ethics of requiring even *one* placebo-controlled trial, let alone more than one, become questionable. (An example would be a new rabies vaccine or antivenom serum.) But there could also be trouble in demanding a second trial when the first has given a clean decision (such as the use of cytosine arabinoside in treating the often fatal herpes simplex encephalitis).

Another example of trouble lies in the inflexible demand that all drugs be required to meet the same standards. Surely old drugs are different from new drugs—would one insist on double-blind, controlled trials for digitalis? The "track record" of a drug deserves some credence. Surely over-the-counter drugs differ from prescription drugs in important ways. Do we really want to demand two controlled trials for every antacid tablet on the market?

What do we do about celery tablets for arthritis? Or homeopathic remedies? Can such medicines simply be controlled by limiting the claims made for them or by identifying them as ancient remedies whose scientific merit has not been proved?

Is it possible, in the case of new remedies, to speed up the approval of new drugs by step-by-step agreement on what is to be done in advance of the clinical trials? Possibly, although one wonders whether such a process might not only delay the taking of the steps but also be flawed by a change of heart on the part of the regulatory agency (or the sponsor) as the data come in.

Concerns about safety are often responsible for delays in the United States. Common side effects are easy to delineate, but the very rare or the long-delayed toxic effects are not. It therefore behooves us to make sure that our demands for hundreds or thousands of additional cases are indeed relevant to what it is we hope to detect. There are many facts about a drug that cannot be known in advance of marketing—drug abuse and the effects of massive overdose are but two. Those should be assessed by appropriate schemes for post-marketing surveillance rather than by holding drugs for ransom prior to registration by extravagant and senseless demands.

Data from industry-sponsored trials often have importance to the sponsor because of the expense involved in generating them and in their value to competitors. However, it is difficult to justify keeping important positive or

negative data from the public, or demanding needless repetition of clinical trials by different firms.

One positive solution to such a dilemma is to make freely available (as is the case already) a summary of data on the drug at the time of its approval. When a patent has expired, it would seem necessary only to insist on human bioavailability data from any new sponsor proposing to market its own version of the drug, rather than demanding new clinical trial data. This approval does not cover all contingencies, I realize, but it should meet some needs. One should not ignore the importance of moves that may seriously diminish incentives to innovation.

Industry has important responsibilities which, if properly discharged, can facilitate the introduction of new drugs. Pharmaceutical companies should choose clinical investigators and research designs of the highest possible quality. Dishonest investigators are rare, in my experience, but incompetence is everywhere and must constantly be searched for. Industry has to stand behind the data it submits, whether the information is generated in its own or outside laboratories.

Findings of data should be put together in a way that facilitates review by regulatory bodies, especially with a view toward distilling the main findings into accurate summaries. Scrutiny of those summaries could eventually substitute for the impossible task of checking every last shred of animal and clinical data.

Drug houses must also criticize and oppose with vigor irrational decisions by Government. It is tempting but unsatisfactory to let unfair or questionable regulatory actions stand, lest battle end up not only with interminable (and expensive) legal wranglings but an abiding distaste at the FDA for the company in all future dealings.

Let me take a few moments to suggest a way of thinking about controlled trials that deserves consideration by Government, industry, and the medical profession. The basic components of my argument are simple:

1. The controlled trial is a mechanism for rejecting the null hypothesis, not for generating conclusions that are necessarily extrapolated to ordinary medical practice. This is so not only because the optimization of circumstances for establishing efficacy may lead to choice of a highly "atypical" experimental population, but also because consent procedures, the reality of availability of patients, and the logistics for their study, etc., all can lead to enormous "volunteer error." Surely no one can pretend that he has ever studied a random sample of the universe of patients suffering from any disease or symptom.
2. This does not mean that the results of a controlled trial are *irrelevant* to the real-life practice of medicine, but it does mean that the results might need modification as one attempts to

apply them to patients who are substantially different from those in the trial. For patients with milder disease, for example, the drug in question may not be needed, not worth the risks, or needed in smaller doses. For patients with more severe disease, the drug may have to be given in higher doses, or may be ineffective at any dose.

3. The obvious conclusion—if you accept the two previous points—is that we must develop new strategies for moving from the "hothouse orchid" environment of most randomized controlled trials to the "field daisy" environment of the practice of medicine.

We have developed the formal controlled trial to a high level of art and science. It has served society well, but it *cannot* do so to answer questions it is not suited to answer. We must move on to the next level of drug evaluation, and to do so may require the talents of individuals who have not in the past played much of a role in deciding whether a drug should be marketed or not.

Finally, a word about guidelines. A number of groups have tried to come up with rules for playing the clinical trial game in different therapeutic areas. To the extent that an area has well-developed, generally agreed-upon methodology, such a spelling out should do some good and cause little harm. Such is not the case when methodology is far from worked out or agreed upon. In any case, rational deviations from official protocols should be encouraged, lest progress in improving clinical trials be stopped.

RELATIONSHIP BETWEEN GOVERNMENT AND INDUSTRY IN CLINICAL TRIALS: NEED AND PURPOSE FOR RULES AND REGULATIONS

Desmond R. Laurence

Regulation of drugs by statute has inherent characteristics that cause the regulatory body to increase its requirements, even where scientific justification is weak, and with little or no regard to cost. The trend to impose safety requirements that are excessive or unbalanced in relation to their cost and to the benefit they confer will continue until health politicians are given an opportunity to sponsor rational regulation without risking damage to their public reputations.

There is increasing opinion that the requirements of current drug regulatory authorities may be excessive and only partly based on science, and that now is the time for radical review and reform. There is a need for:

1. Evaluation of benefit/risk/cost by independent scientists internationally.
2. Availability to those who suffer adverse effects of new drugs, not only in premarketing research but also during any period of postmarketing surveillance, of a speedy, efficient, and generous "no fault" or "strict" liability system to compensate for drug-induced injuries.
3. Continuing explanation to the public and to politicians of a balanced picture of benefit/risk/cost of drug research and development.

To state the purpose of government rules and regulations controlling development and introduction of new drugs is simple: to protect the public against risk, exploitation, and incompetence. In such an area, where action must inevitably infringe the liberty of several parties (developers, doctors, and patients), Government has waited for the need for intervention to become imperative before it has acted. Although the United States learned its lesson in 1938 with the Massengill/sulfanilamide accident, most of the world introduced comprehensive controls only after the thalidomide disaster of 1960-61.

In the United Kingdom we are still using what is essentially the same procedure as that developed in haste and inexperience after thalidomide, although it has since changed from a voluntary to a statutory system and has added concern for efficacy to that for safety. Eighteen years after that disaster is an appropriate time to look at our regulation, its characteristics and extent, and to ask ourselves whether we have developed an efficient benefit/risk/cost system.

As an independent adviser, I joined the old voluntary organization for drug

regulation, the Committee on Safety of Drugs (Dunlop Committee), in the year of its establishment (1964). I served until it was translated into the statutory Committee on Safety of Medicines in 1971 and saw the changes in attitudes and practice that accompanied the imposition of law. Over the years I have been involved in the debates on what regulatory action should be taken on all the problems that, sometimes with dramatic suddenness, are put before a regulatory body. I have now left the interest, excitements, tediums, and frustrations of the Committee on Safety of Medicines for the supposedly higher levels of regulatory policy, the Medicines Commission. One of its first tasks under the Medicines Act of 1968 was to advise the Secretary of State for Health that a Committee on Safety of Medicines should be appointed to succeed the previous voluntary arrangement. I am here going to argue that our present system of drug regulation is not as efficient as it should be, and I am going to offer for discussion some reasons why this may be so and some proposals as to what might be done to improve it.

I shall take it as common ground that some form of government regulation of drug introduction is both desirable and necessary. My theme will be as follows:

1. That regulation by statute has inherent characteristics that cause the regulatory body to increase its requirements, even where scientific justification is weak, and with little or no regard to cost.
2. That the trend to impose safety requirements that are excessive or unbalanced in relation to their cost and to the benefit they confer will continue until health politicians are given an opportunity to sponsor rational regulation without risking damage to their public reputations.
3. That current drug regulation is excessive and only partly based on science and that it now requires radical review and reform. To achieve this we need:
   a. Evaluation of benefit/risk/cost by independent scientists who are not merely experts but authorities (I use the distinction of Melnick et al. [1]).
   b. Availability to those who suffer adverse effects of new drugs, not only in the premarketing research but also during any period of postmarketing surveillance, of a speedy, efficient, and generous "no fault" or "strict" liability system to compensate for drug-induced injuries.
   c. Continuing explanation to the public and to politicians of a balanced picture of benefit/risk/cost of drug research and development.

Problems of Statutory Regulation

In 1964 the newly set up Committee on Safety of Drugs told industry that in effect the committee intended to operate in a liberal and understanding fashion, that it was a body of reasonable people whose only desire was to protect the public, and that it would only be necessary for drug developers to put forward reasonable proposals. Although the intention was applauded, this statement was, of course, no use to industry as a way of conducting their practical affairs. Much of drug testing, especially safety testing, is a matter of opinion. Industry could not afford to risk being told, after completion of years of work, that the committee felt, for example, that the chronic toxicity tests should have been done differently or more extensively and that the applicant should start again. Requests that a plan of research for individual projects be approved in advance were, naturally, declined as impractical by the committee. The result was the committee's first set of guidelines, which were careful to indicate then, as now, "In the interpretation of the following guidelines it must be appreciated that they are not rigid requirements and may not be universally applicable. Interpretation should therefore be flexible and related to the proposed use of the drug."

Guidelines inevitably become close to minimum requirements. A developer who does not follow them does so at peril to his research program. In the face of an adverse decision, appeals to stated intentions of flexibility may indeed succeed, but they may fall on deaf ears. Advisory committees have their moods; sometimes matters of opinion and of judgment are decided differently on different days. Everyone knows that this must be so, although it is not widely spoken about; it is, no doubt, one of the reasons why we have a good system of warning applicants of impending adverse recommendations and of appeals. It is a bold or rash research director who does not tell himself that prudence counsels the performance of tests mandated by the guidelines, even where he or she doubts their value. The expense of a regulatory setback can be greater than the expense of extra tests.

As time has passed industry has asked more questions on toxicity testing, species of animals to be used, doses, duration of tests, oncogenicity, mutagenicity, clinical trials; the list is extensive. The committee has responded as it should, with detailed decisions where appropriate. For the broader areas it has set up working parties jointly with industrial scientists to prepare guidelines.

The meetings of such working parties are not divided into industrial workers seeking to minimize requirements and academic and other scientists seeking to maximize them. It is my experience that for specialist scientists the interest of the application of their expertise to the fascinating process of prediction from animals to man arouses enthusiasm that overcomes any loyalties to employers incompatible with their science. I have been interested to see industrial scientists willingly imposing on themselves the burdens of dubiously predictive tests, particularly in areas of reproduction and oncogenicity. The result of all this is a relentless ascending spiral of requirements as knowledge of what *can* be

done and of what *may* happen advances. Testing for reproductive function provides an example. In 1964 we expected dosing of pregnant animals only during the period of organogenesis; now we expect to start dosing both sexes before mating, to continue throughout pregnancy, to wean the litter, to rear some, and to breed from them. In addition, events occur and problems arise that conspire to increase testing requirements; for example, problems of oncogenicity and the oculomucocutaneous syndrome of at least one beta-adrenoceptor blocking drug, problems with renal toxicity of nonsteroidal anti-inflammatory drugs, etc.

Another issue of increasing importance in preclinical testing is the ethical aspect of employing large numbers of animals in tests of doubtful relevance to man. There is growing opinion among those who are not opposed to all tests in animals that their use should be confined to areas demonstrated to have relevance to man. At present in the United Kingdom there is a demand for Government to sponsor an inquiry into the need for and amount of research conducted in animals. We should not ignore this concern.

In the special area of clinical trials I shall discuss three examples of aspects where disagreements have arisen between regulatory bodies and those within and without industry who develop and test drugs.

First: The extensive requirements in the United Kingdom for pharmaceutical, chemical, and analytical data before clinical trial, which industry has long criticized as unnecessary. Industry notes that these areas are under development and that extensive detail is not available and is even considered unnecessary by other countries. Clinical trials of drugs developed in the United Kingdom have often been well under way in other countries, while the U.K. authority "is still querying details which are, at best, on the borderline of relevance" [2]. Debate in this area persists. There is a genuine difference in what the two sides consider to be necessary for safety.

Second: Recently concern arose in the regulatory body because some developers were submitting applications for marketing drugs (product licenses) for indefinite use in man, e.g., antihypertensives, on fewer and fewer patients treated for shorter and shorter periods. A discussion followed as to reasonable size and duration for clinical trials of such drugs. The consensus was that, to prepare a good medical data sheet on efficacy, dosage schedules, and the more common adverse reactions, it would be desirable to have treated about 100 patients for about 1 year. The regulatory body's sole objective was to help drug developers plan their studies and avoid premature applications with their consequent waste of time and effort. But when this view was intimated to industry, there was an outburst of indignation about excessive and arbitrary regulation being imposed without consultation.

This incident occurred at about the same time as a proposal from a working party on oncogenicity testing that no drug should be given to human beings for longer than 6 months unless it had undergone standard oncogenicity tests. In

other words, if clinical trials are not to be interrupted at 6 months and re-started later, some oncogenicity studies will have to begin before it has been decided to give the drug to man.

It is easy for a regulatory body to find itself in situations of this kind resulting from advice of different expert groups. Although I have no doubt this particular problem will be solved by discussion, it underlines the increasingly recognized need to take a hard look at the scientific basis of drug regulation in relation to the practicalities of the process of drug development and its social importance.

Third: The proposed FDA regulations on clinical investigations address the obligations of sponsors and monitors [3]. In 1976 the FDA was allocated $16.3 million and authorized to appoint 600 new staff members (the European mind reels at these figures) to expand monitoring of preclinical and clinical research related to FDA-regulated products.

My reason for discussing FDA activity here is that its proposals will apply to other countries if data generated outside the United States are to be accepted by the FDA. The drug industry is international, and it is vital that data be accepted internationally wherever scientifically appropriate. (The new group of histamine H_2-receptor blocking drugs was discovered and developed in the United Kingdom, but researched in the laboratories of an American drug house.) Some proposed regulations may have to be modified where conditions in other countries are so different that some aspects of the FDA regulations cannot be applied.

The general intentions of the FDA are above reproach. Of course, bad clinical studies are done, there have been cases of falsification of data (in both our countries), and we do ignore pompous people who are insulted if they and their work are scrutinized. The FDA preceded their regulations with a survey of clinical investigations (concluded in 1974) that found, as expected, that "grossly violative practices are infrequent, minor deficiencies were frequent." Yet we hear in 1978 that there is enough concern for the FDA to mount a further investigation.

Monitoring of clinical studies is proposed in quite extraordinary detail. I cannot help wondering who the monitors will be, for if they are incompetent we are better without them, and if they are competent they have skills that could be better employed.

In the early days of motoring some governments decided that in the interest of public safety close monitoring was required. Each car was preceded by a man with a red flag. No doubt this prevented speeding, but it was soon abandoned. We all know the terrible current loss of life on the roads, and we all drive with more care for the regulations (and perhaps even with more skill) when we know we are being monitored by a policeman. Why does no one advocate that each car on the road be monitored by a police car? We all know why. There is a lesson here for drug regulation.

We limit the policing of society because it is expensive and because the public can see for itself what it involves and tell the politicians what they want in relation to benefit/risk/cost. But drug development is not so easily comprehended by the public, and the checks to overpolicing do not act.

I have referred in passing to the moods that can affect committees and to the enthusiasms that affect experts whose advice is sought. Plainly, the tendencies of drug regulation cannot be spoken of as if they were independent of the individuals who conduct the business. After forming these views I shall express here, I was interested to read an article by Lord Ashby [4] that explained the background to what I had been experiencing, in taking decisions we are influenced by the desire not only to avoid risk but also to avoid regret later: "risk avoidance" plus "regret avoidance."

There are certain important characteristics to governmental regulation of drugs in the United Kingdom. The minister responsible:

1. Can be questioned publicly in Parliament.
2. Is obliged to depend for his reply on civil servant and expert advisers.
3. Receives no credit when a good drug goes into general use, but can receive severe criticism when an accident occurs.
4. Does not find any important political principle or party advantage in good drug regulation.

It would be a matter for surprise if in these circumstances not only the politicians but also the civil servants and expert advisers find themselves seeking to minimize risk, although it might not seem so to them as they work. This innate tendency toward immediate risk avoidance can be further enhanced by the desire to make recommendations that will also not be a subject of later regret, "regret avoidance." The pressures of risk avoidance plus regret avoidance are real and can lead to suffocating overregulation. As Ashby [4] remarks, "neither politicians nor the civil servants advising them like making enemies; their temptation to indulge in regret avoidance is strong, . . . the decision-maker himself is liable to have an instinctive bias to risk aversion and dilution of responsibility."

The kind of continuing pressure on drug regulators was illustrated within a few months of marketing of the first histamine H_2-receptor blocking drug, cimetidine (Tagamet) by a Member of Parliament's publicly asking the Secretary of State for Health about adverse reactions to the drug. There was no public anxiety about this drug, and a parliamentary question of this kind is unusual. The politician could easily have gotten the information privately from the developer or from the Committee on Safety of Medicines; but for reasons I cannot fathom, he chose to get it publicly in Parliament. Inevitably those in drug regulation as well as drug development are affected by the knowledge that they are being watched closely by people ready to criticize at any opportunity

but whose motives are not always obvious. "Miracle" drugs are a media wonder for a day or two; their hazards provide material for months, with scope for moral indignation added. But workers in drug regulation, independent advisers as well as civil servants, can never forget how they came to be where they are. Their prime function has been protection of the public through smooth operation of the law and such detailed policies as are formulated by the regulatory organization to carry out the intention of the law.

I myself have a clear recollection of saying with emotion at a meeting of the Committee on Safety of Medicines, "Let us remember that it is thalidomide that brought us round this table, and let us remember our title, the Committee on *Safety* of Medicines."

It is also true that the atmosphere in a decision taking committee with detailed data on particular chemicals before it is very different from the atmosphere in a general discussion on the philosophy of benefit/risk carried out where there is no immediately pressing question of making a decision affecting the safety of individuals. The risk of public outcry if a wrong decision is made adds to this dilemma.

Continuously sitting in judgment on the laborious work of others carries an occupational risk of developing unrealistic standards. It is too pleasant to be able to demonstrate to colleagues that one has a razor sharp mind that never misses deficiencies and always thinks of better experiments; that one has high standards that cannot be compromised; or that anyone who advocates less has low standards, is the victim of sloppy thinking, and might even be callous to human suffering. Certainly pressures form our attitudes, and those undertaking the responsibilities of drug regulation are subject to these pressures and are influenced by them whether they are conscious of this or not. Despite these pressures, regulatory bodies should seek to smooth the path of valuable new drugs and even to explain to the public that benefits exact a price in risk since they represent relatively new ideas.

Rational Regulation

It is often claimed that politicians will seek absolute safety in drug testing and will demand that all thinkable precautions be taken, regardless of whether there is in fact good evidence that those steps contribute to safety. Certainly the natural tendency of people who are publicly accountable is to act to avoid any possible criticism in the future (risk avoidance and regret avoidance). But politicians do know that absolute safety is unattainable, even if they seem to behave otherwise.

In 1963 in Parliament, discussing the setting up of the Committee on Safety of Drugs, the Minister of Health stated "emphatically that when they used the word 'safety' . . . they should not be understood to mean 'absolute safety.' Safety in this sphere was relative whatever might be the arrangements, whatever might be the law. It was relative to the illness, and . . . there was no system

that could be devised which would make doctors or scientists aware of what medicine and science had not yet suspected" [5].

Politicians naturally rush to fulfill the expectations of the public on whom their careers depend; and they respond to what they interpret as pressure from the public in general, although that pressure is largely the result of efforts by special interest groups and the mass media. If we want politicians to act sensibly in areas where there is public anxiety and outcry, they must be protected from unreasonable criticism. Their path must be made easy, or they will not act sensibly.

I suggest that it will be politically impossible to do other than to maintain or increase regulatory requirements along current lines until health politicians are convinced that there is public understanding and acceptance of the need for review and change. The public must accept the fact that risk is inevitable and that it is in the interest of the sick that certain risks be taken. This means that the mass media, representing the public, must accept and propagate the attitude that risk is inseparable from drug development and use and that the risks of drugs are as socially acceptable as risks of surgery, and a great deal more acceptable than the risks of smoking and alcohol. This is a task for scientists with a flair for communication. But they cannot succeed unless one special condition is met.

The public attitude toward industrial drug developers must be changed and be separated from that of the multinational corporations, which have a bad public image. I am concerned here only with drugs.

It is relevant that in the United Kingdom elected Members of Parliament were active leaders in associations of patients that negotiated, in a blaze of publicity, compensation for victims of thalidomide. More recently (1976) in the case of practolol, where the initial offer of the company preceded any outcry, this did not prevent a similar process during which the compensation was considerably raised. It seems unlikely that it can ever be acceptable to leave it to the pharmaceutical firms to set up or handle processes of compensation. The apparent need for associations of damaged patients has had a big effect on public attitudes. Such associations must be made manifestly unnecessary, and that will only be achieved if the public can see that the pharmaceutical industry accepts liability for any casualties of its development activities and that the decision to compensate and the amount of compensation are delegated to independent assessors. Indeed, schemes for "strict" or "no fault" liability for manufactured products, including drugs, are being introduced in many countries and are expected in the United Kingdom. The pharmaceutical industry has generally accepted that this is a responsibility it must meet.

Review and Reform of Drug Regulation

To achieve radical review and reform of drug regulation in light of current science and the experience of the past 18 years we need:

1. Evaluation of benefit/risk/cost by independent scientists on an international basis (for drug research and regulation is now an international activity) considering what is necessary and, equally, what is not necessary.
2. Availability to those who suffer adverse effects of new drugs, not only in premarketing research but also during any post-marketing surveillance, of a speedy, efficient, generous "no fault" or "strict" liability system of compensation for drug-induced injuries.
3. Continuing explanation by scientists to the public and to politicians of a balanced picture of benefit/risk/cost of drug research and development.

If these three conditions are met, we can have some hope that it will become politically possible to base drug regulation on scientific considerations alone. It is in the public interest that this be achieved.

There is evidence from many sources of growing concern among scientists that drug regulation may be suffocating new drug development and that it is desirable that independent scientists play a greater part in formulation of national policies. This evidence stems from various sources including Dr. Lasagna's Center for the Study of Drug Development [6], industrial scientists [7], university biological and political departments [1], and European academic and industrial scientists [8].

It is known that official regulatory organizations are engaged in regular consultation internationally in Europe (European Economic Community, Council for Mutual Economic Assistance, World Health Organization European Region [9] all have annual meetings), and across the Atlantic. At these meetings the tendencies that I have discussed are operative. The official drug regulators have access to funds for regular meetings.

International scientists independent of government service certainly meet each other from time to time and they recognize the problems, but there are no regular meetings that allow systematic reviews and the development of new, rational policies.

Jack [7] categorizes risk in formal clinical studies as relatively low in the early restricted and carefully monitored stage, intermediate in the late formal clinical trials, and high after marketing, when the drug is used in a larger, heterogeneous population with less supervision. This is a generally accepted view. He points out that British regulatory procedures are not consonant with this: they are more detailed where the risk is low and less detailed where it is high.

Nobody objects to strict regulatory requirements if they are effective. For instance, the need for postmarketing surveillance is now generally accepted, but it looks as though regulatory bodies are going to add it to the edifice of existing requirements without review of whether its institution could be

accompanied by some relaxation in the lower risk areas. We cannot afford to continue expensive practices that are not efficient. A colleague remarked to me recently that if all drug development were done in government laboratories and paid for with tax monies, there would be urgent discussions on whether value for money was being received from escalating budgets. But the testing takes place in private industry, and global figures are not available or are not in the right form, so no such concern on cost/benefit is shown. There is a general feeling that drug prices are too high, so it is the public who pays the bill in the end in both cases.

Melmon [10] made two remarks in his article that are particularly relevant to my purpose. He writes that he considers that academicians can and must help to create sound legislation and assume authority in scientific matters. He adds that his disappointment is not with Government but with scientists and their inaction. He is right; Government is a sailing ship that has been following the strong wind caused by public reaction to thalidomide. It is only likely to change course if a new wind of science blows from a different direction.

Melnick et al. [1] make a useful distinction between an "expert" and an "authority." An expert is recognized by his peers; an authority is one whose expertise is recognized outside the scientific community, one who is called on to give advice and counsel to the public. It could be said that many experts are now vocal, but they still have not seen their way to influence Government directly and via public opinion, as Melmon advocates. This will be achieved when more experts become authorities (as defined above), for unless they do we shall see bad policies continuing to the accompaniment of experts wringing their hands. People who actually labor and take the responsibility for developing and testing drugs and choosing and using them to treat disease are the people who should set the standards for drug regulation. If there are grounds to fear that there is overregulation, these are the people who must go out and influence the public and Government. When public expectations are in accordance with reality we shall have good drug regulation, not before.

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DISCUSSION

Robert J. Temple

The discussion following Dr. Lasagna's and Dr. Laurence's talks focused on the evidence required before a new drug may be marketed and, specifically, on the case of sodium valproate as an illustration of some of the differences between the United States and the United Kingdom and of the judgmental elements that are always part of such decisions.

Dr. Booth took issue with Dr. Laurence's discouraged view of the British legislation, urging that this relatively recent legislation be given a chance to "go" for a while before major changes are attempted. He felt the new legislation, while not perfect, was a vast improvement and had led to strong and effective international relationships with the United States and Canada through the tripartite agreement.

Dr. Laurence denied suggesting that legislation needed to be altered. The legislation, he noted, simply says that the efficacy, safety, and quality of drugs shall be controlled; it does not say how that should be done. He felt the requirements under the legislation, however, were escalating and were going too far. The cost of developing novel chemicals is about $55 million, and probably only 22 firms in the world can contemplate that "with reasonable equanimity." Under the existing legislation there is a tendency to "add, add, add," which is probably not scientifically based. It is this pattern he would like to see altered, not the legislation itself.

This point was echoed by others. In response to a question by Dr. Chalmers, Dr. Lasagna agreed that, as "someone who. . .played a small role in helping to get the '62 amendments passed," he was appalled at any movement to repeal the effectiveness provisions of the Food, Drug, and Cosmetic Act and considered such a move as unneeded, as were efforts to give new powers to the FDA. Rather, he believed the act was generally a good one, although not perfect. He said he found most of his arguments with the agency had to do with implementation and regulation. He knew of no reputable academic clinical pharmacologist or drug industry leaders who had advocated repeal of the law.

The discussion then turned to Dr. Ryan's question regarding possible expedited approvals and the recent public clamor for sodium valproate, which had been unavailable in the United States despite a general view that it was effective. Dr. Lasagna found himself both encouraged and discouraged by the valproate, Laetrile, and saccharin episodes, each of which showed that the public can become aroused and impassioned and begin to say to regulators, industry, academia, the medical profession, and Congress, "A pox on all your houses. We don't trust any of you. Tell us the facts, but don't tell us what to

do." Although he found that situation encouraging in a democracy, democracies do make errors. Thus, while he thought Congress made the correct decision on saccharin, he could not be encouraged by the Laetrile episode. While he felt valproate had been well worked up and deserved "expediting," he warned that if a deserving drug can be expedited, so can an undeserving one. While he realized FDA would say it would not approve such a drug, FDA is subjected to constant political pressures, especially from Congress, and he therefore remained concerned.

Dr. Temple explained that valproate had been denied approval initially because the statutory requirement for well-controlled studies showing effectiveness had not been met. Shortly after that decision, other studies were completed, and the drug was approved. Dr. Ryan's question was whether approval could have been granted earlier, when "everyone knew" valproate worked but controlled studies were not complete. Under present law the answer is no. Legislation now before Congress, however, would, under very specific and limited circumstances, permit different kinds of evidence (i.e., evidence other than well-controlled studies) to be a basis for provisional approval of a drug for marketing. This would apply only to drugs that are lifesaving or intended for an extremely serious illness, and the drug would have to have a tremendous advantage over other kinds of therapy. Under such conditions, the drug could be approved, and well-controlled studies performed afterward. This feature of the law may help resolve the problem of the drug that is known to work but cannot yet meet the statutory standard; it clearly raises, however, the concerns Dr. Lasagna described.

Dr. Laurence pointed out that Britain had marketed valproate on the basis of studies available, which were considered adequate. He found the difference in judgment interesting. Britain felt there were reasons to think it was effective in patients not controlled on other agents. Studies were confined to this population, and general studies in epilepsy were not required. Yet, the same studies were found inadequate by the United States. He wondered whether this was an example of having a general rule of what constitutes an adequate study and then applying it across the board to absolutely everything.

Dr. Lasagna added that it appeared new chemical entities for which applications are filed almost invariably get approved eventually. He thought the delays are due to arguments about what constitutes enough evidence of efficacy and safety, which is where men of good will can disagree. He also felt this judgment was flexible in some cases, suggesting that valproate was pushed along faster than Dr. Temple's discussion implied because of the "impressive media work" backing it.

Dr. Crout of the FDA then sought to clarify the sodium valproate situation, which he viewed as a classical example of the difference between decision-making on the basis of expert opinion and the FDA's evidentiary standard of the adequate and well-controlled trial. He agreed that there was a great deal of political and media pressure and this had had two effects: first, it persuaded

Abbott Laboratories to move its own research program along and get a new drug application together; second, it caused the FDA to expedite its review. What the FDA sought to avoid, and did avoid, was changing the evidentiary standard, because the FDA "feared the specter of any number of drug firms seeing that the combination of publicity, an outside pressure group, and congressmen writing can erode standards for drug approval." The FDA and Abbott thus tried to move fast, but the FDA also tried to be "as picky with valproate as we are with all drugs."

After the FDA received the valproate application, it was taken very promptly before that agency's advisory committee, which unanimously recommended approval of the marketing application because the committee members thought the drug worked. Everyone in the FDA agreed that valproate was an anticonvulsant and that it worked. But when the studies submitted were compared with the standards of a well-controlled study, the studies did not meet criteria that had been set up by the same advisory committee. For example, the committee had previously said (in its anticonvulsant guidelines) that anticonvulsant drugs should be approved for specific types of epilepsy, because different anticonvulsants had different effectiveness in the various types. Petit mal seemed the type for which valproate was likely to be best. But when the FDA looked at the few controlled trials of the drug (valproate had been worked up in France in the late 1960's and early 1970's, and most studies were uncontrolled), there often were very few cases (six to eight) of petit mal. These trials usually compared valproate with a positive control, ethosuccimide; and six to eight patients is very small for a positive control trial. Often, concomitant medication was present, which can also be a problem. For example, valproate leads to increased blood levels of phenobarbital; it appeared possible this increase, rather than the valproate, might explain improvement seen. By the time various cases and trials were dropped for various reasons, "the trials fell apart." It was not that the trials were wrong; they could not meet modern evidentiary standards. The FDA thus had an advisory committee recommendation for approval, but a recommendation that did not identify any adequate and well-controlled trials. The committee had provided "a conclusion without the supporting evidence," the worst kind of advice you can get from a committee when faced with a "hot" problem. The FDA asked for another trial, which fortunately was under way—a telemetry-monitored trial, and a good one. The data came in January 1978, and the drug was approved in February. Dr. Crout explained that he had provided the details of valproate so the group could get "a feeling for some of the agonizing over trials and some of our attempts to be very precise on the evidentiary standard because valproate signifies. . .the crux of the difference between the United States and the United Kingdom in its decision-making."

Dr. Laurence suggested that the FDA was "a prisoner of [its] good intentions. . .you explained it absolutely perfectly. . .it was a good drug and with lots of evidence but [the evidence] was not of exactly the right kind. . .so you

say 'we can't act.' " Dr. Crout explained that it was a greater failure than "not exactly the right kind." When the cases of petit mal were collected there were so few that in a positive-control study (evaluating sameness, not difference) the statistics do not permit a conclusion that a lack of difference was demonstrated. Dr. Crout emphasized that the FDA had not "invented some fake standard." Valproate did not meet the prevailing standard. Once the proper data were available, valproate was approved, and in less than the 180 days allotted.

Dr. Laurence explained that the United Kingdom also had seen "the problem of the French evidence" and had asked for a small, careful trial in patients inadequately controlled by current therapy. The trial came out positive very quickly.

Dr. Crout explained that FDA had seen a similar trial. Patients resistant to ethosuccimide were randomized to valproate or ethosuccimide. If they did not respond to the initial drug they were crossed over. Unfortunately most of the patients given ethosuccimide responded to it, even though they supposedly were resistant. Thus the entrance criterion had not worked properly.

Dr. Lasagna found this incident "surrealistic." He felt that if an advisory committee, to a man, says a drug is effective and the official criteria are not met, you have either bad advisers or bad criteria.

Dr. Crout disagreed. He quoted Otto Warburg as saying, "I spend 10 percent of my time convincing myself of what the truth is and 90 percent convincing everybody else." The U.S. regulatory standard of adequate and well-controlled studies requires trials to be documentary. The requirement may go beyond the required amount of documentary evidence that is usually necessary to convince an expert that something is working. Our advisers generally bring to their decisions their experience and intuition and would routinely approve a drug in their area before the evidence is all in, although they might want to limit it to certain experts.

Dr. Lasagna responded that if the advisers are generally wrong the requirements for additional evidence are well taken; if, on the other hand, they are almost invariably right, one wonders whether the requirements for evidence are not excessive.

Part 8

INTERNATIONAL STANDARDS IN CLINICAL RESEARCH

C.C. Booth

Internationalism is more than an encounter between European and North American peoples; it reflects the meeting of peoples of different cultures that leads to greater understanding. Science provides the international forum where all peoples can meet on equal and common ground. In the field of medical research, internationalism is fraught with both political and scientific difficulties, and we in the West often end up branded as scientific or medical imperialists.

Internationalism in medical research is promoted by the same forces that disseminated the early findings of medical science (although some have broader implications because of modern technology): clinical research, common language, medical societies and journals, and control of health services and medications. We in the West, however, must not overlook the fact that what is good in one environment might not suit the environment of the developing world. It is important not to lessen the spirit of internationalism by overlooking the needs and desires of developing countries.

Internationalism has been the utopian dream of idealists ever since the confines of the existing world became more generally known in the 18th century. In December 1780, Benjamin Franklin received a letter in Paris from his one-time London physician calling for the "institution of a college of justice where the claims of sovereigns should be weighed, an award given, and war only made on him who refused submission. . ." [1]. The past 200 years have not yet realized this dream, and current events in the eastern Mediterranean region and elsewhere should remind us that nationalism rather than internationalism will guide the destinies of the peoples of the world for many years to come. In the devolutionary world in which we live in Europe, where Basques, Scots, Bretons, and Welsh all seek their own narrow nationalism, we could be thought to be departing from the united Europe envisaged by Maurice Schuman. Yet although this is true to a certain degree on the political scene, it can also be emphatically stated that in medical research there has been during the past 10

I am particularly grateful to Dr. E.L. Harris of the Department of Health and Social Security for his assistance in guiding me through the Medicines Act of 1968 and the work of the Medicines Division.

years an important "rapprochement" in the countries of Europe, and not just in the European Economic Community. This has also been true all over a world where air travel has made neighbors of once distant and alien peoples.

When we talk of international standards in clinical research we must first define our terms. What is *international?* What do we mean by an *international standard*, and what is *clinical research?*

Internationalism

To me, internationalism means a meeting of peoples of different culture, not merely an encounter between European and North American people who share the same cultural background and who, therefore, have a solid base for mutual understanding. The North American experience was created out of that policy so well enunciated by Tom Paine when he pleaded that America should give up dependence on a small island 3,000 miles away, cut itself off from that "Royal Brute of Great Britain," and claim brotherhood with every European Christian. Like so many of his countrymen at the time of the Revolution, he ignored the Jewish contribution to the cultural identity of Europe and North America; he might well never have known of Chaim Solomon. But the policy that he advocated created the greatest of the world's modern republics.

What now is important in the international scene is that Europeans and North Americans meet and understand Indians, Africans, Chinese, and Arabs, for example. For among these people, with ideas of life and the world so different from ours, there are differences in wealth and culture that are significant in dividing the globe into those areas so facilely classified as "developing" or "developed." Surely, it will be said, science (particularly medical science) provides an international forum where all peoples can meet on equal and common ground. To a Westerner, this seems axiomatic, but the science of Western man represents something that has long been part of his cultural heritage, derived from Greco-Roman origins, from the Arabs who maintained the light of knowledge in their places of learning during the Dark Ages in Europe, and more recently from the Renaissance and the Industrial Revolution. Others, however, who do not share this cultural heritage reject the Western materialistic concept of life and often reject with it the achievements of medical science, not because they do not understand it but because they see it as a dangerous imposition of part of an alien culture. Such attitudes are not uncommon in some parts of the developing world today, where international understanding is vital in achieving the common goals of eradicating or controlling poverty and disease.

International Standards

International standards, like any other standards, can be considered in terms of either quantity or quality. Quantity standards do not present any great problem in international terms. In the medical field organizations such as the

World Health Organization have been particularly effective. Hemoglobin standards, for example, are now internationally agreed, and in the particularly important area of biologic materials (vaccines, antibiotics, and other such products) a great deal has already been achieved through existing machinery to ensure that knowledge is internationally available and immediately accessible. Perhaps the most important achievements here have been in the international control of infectious disease, in particular, the eradication of smallpox.

It is, however, in the quality of research that the real difficulty lies in the international field. Here we are often dealing with matters of opinion rather than matters of precise measurement. What standards, therefore, do we accept? In many countries individual scientists have their own ideas on what is best. For many clinical scientists the ultimate accolade is to have one's work published in the *Journal of Clinical Investigation*, a reflection of the leadership in scientific and technical matters that the United States at present enjoys. But if the Western European countries and North America agree on particular standards, and there is evidence from the award of Nobel Prizes that they do, do they expect the developing world simply to accept those standards and seek to emulate them? In the field of research on drug treatment such an approach is fraught with both political and scientific difficulties, and we in the West often end up branded as scientific or medical imperialists.

Clinical Research

Clinical science was a development of the Renaissance in Europe; its leading protagonist was William Harvey [2]. Sir Thomas Lewis wrote that clinical science comprised three main streams of investigational activity—the study of living men in health and disease, studies of pathology in the autopsy room, and correlated studies undertaken in lower animals where necessary. Few people recognize that William Harvey used all three of these lines of inquiry in his classical studies of the circulation of the blood. In addition to his beautiful physiological studies in animals and in man, Harvey used clinical observations to illustrate that the blood must circulate [3]. For example, he cited the case of fever and other dread symptoms coming on long after the wound made by a mad dog had been cured, a situation in which he said the contagion had clearly entered the blood stream and in passing through the heart and circulation had polluted distant parts of the body. Lewis thought, as I do, that "De Motu Cordis" represented a "romantic example of scientific exposition unsurpassed in his time and since his time" [2].

How did Harvey's work become internationally known and ultimately accepted, and is the process of dissemination of knowledge any different today? Harvey in fact began in his own country giving demonstrations of his work as many might do at a scientific meeting today. Then he had the opportunity of lecturing on his theories at the Royal College of Physicians of London. Finally he published his work in Frankfurt in Germany in 1628. The

language that he used was Latin, which all scientific men of that era could understand.

Language

What changes have affected clinical science since the time of William Harvey? First, there is the question of language. Latin has now been virtually replaced by English as the *lingua franca* of the scientific world. This means that for all those whose mother tongue is not English, their second language must be English. It equally means, since man is inherently idle in linguistic terms, that those who speak English as their natural language have no incentive to learn other languages. This is resented by those who do not speak English, and there has been a particular problem in the West between the Anglophone and Francophone communities. It is a problem that can only be solved if the Anglophone countries and their educational authorities accept that they have a duty to international understanding to speak at least one language other than English fluently.

Medical Societies

The second development since Harvey's time has been the growth of medical societies. Starting in the 18th century these societies initially were small gatherings of medical men who came together in a city such as Edinburgh or London to discuss problems of mutual interest. This century has witnessed an enormous expansion of the medical society, and in recent years there has been the development of the huge international gatherings that are so popular a feature of the jet-set scientist's life. For scientists, however, the wheel has now turned full circle. Instead of participating in the massive international meeting, held usually at 2- or 4-year intervals, many now opt for the small meeting similar to those of the early medical societies where numbers are limited and where discussion can be free and uninhibited. Such meetings have been the major contribution of the CIBA Foundation in recent years.

Medical Journals

More important to the international scene than the development of the medical societies has been the growth of medical journals. They often started as the proceedings of the small medical societies of the 18th century. In Edinburgh, for example, the *Medical Essays* were published from the 1730's onward, and a group of Edinburgh-trained physicians working in London produced the *Medical Observations and Enquiries* between 1752 and 1784, the first medical periodical in England. The modern medical journal, with its system of peer review, represents the most effective medium for the maintenance of international standards in clinical research. At the same time many English

and American journals, although national, have become international in their scope; this has been not only a reflection of the international use of the English language but also a result of the favorable public and political attitude to the allocation of resources for medical research in the United States, Britain, and the Scandinavian countries.

Health Services

Perhaps the major influence on clinical research during the present century has been the development of health services funded from government sources. Such services vary in quality, and there is a considerable variation in the way in which health is approached in different countries. There are important differences, for example, between the provision of health care in the communist economies of Eastern Europe or the Soviet Union and in the mixed capitalist/socialist economies of Western Europe. In China the development of the barefoot doctor concept, so reminiscent of the medical assistant who was the linchpin of medical care in African countries in the heyday of British imperialism, has had important implications for countries such as Tanzania. More important for medical research has been the increasing demand by politicians who control the finance for relevance in clinical research, an outlook best exemplified by the Rothschild doctrine in Britain and by the Nixon initiative on cancer in the United States. The implications of these developments necessitate constant surveillance by scientists themselves, and it is important that international channels of communication be maintained and encouraged.

Control of Medicines

It is in the field of drug control that the establishment of internationally accepted standards in clinical research is perhaps most attractive. For the moment, however, it seems unlikely that a formal international agency for drug control can be considered desirable if only because the control of drugs is a national rather than an international question and is governed by national law. In the United Kingdom, for example, it is the Medicines Act of 1968 that controls "medicines." Under this act a Medicines Commission was established, together with a series of statutory advisory committees. They include the British Pharmacopoeia Commission and the Committee on Safety of Medicines, which includes subcommittees on Toxicity and Therapeutic Efficacy, Chemistry, Pharmacy and Standards, Biological Materials, Herbal Products, Adverse Reactions, and Antibiotic Substances [4]. Within the Department of Health and Social Security there is a Medicines Division with 230 staff members, including 18 physicians, 51 pharmacists, 19 scientific officers, 4 lawyers, a dental officer, and 120 administrators [5]. This sort of organization is duplicated in many Western countries and is an absolute necessity for administering the national laws relating to drug control. Clearly such an organization can

accept evidence on drug trials from any part of the globe; and, in general, most countries now accept on an international basis properly conducted studies of the effect of drugs on animals.

It is in human studies that there is clearly a continuing need for national rather than international control. The reason for this is not just narrow nationalism but the biological differences that exist between different people in different cultures. A drug given to middle-class shopkeepers in Boston or Glasgow might be metabolized differently than in a group of Japanese individuals of similar status. In human studies there is, therefore, a compelling need for nationally organized trials.

It is, however, important that there be efficient, continuous communication between the national authorities in different countries. In Britain there are formal links between the national agencies and WHO, the European Economic Commission (EEC), and the Council of Europe. Britain is also a signatory of the Convention for the Mutual Recognition in Respect of the Manufacture of Pharmaceutical Products together with a group of other European countries, most of which do not belong to EEC. Of special importance to British officials is the unofficial and informal communication constantly maintained between them and their opposite numbers in the United States and in Canada. There is clearly a vital need for international communication, but there seems at present no particular requirement for an international agency for the control of medicines or clinical trials.

Developing Countries

This state of affairs has important consequences for the developing world. The control of most medicines and their manufacture lies with the developed countries of the Western world. If, therefore, a drug such as a contraceptive pill is produced but banned by a Western country because of an infrequent hazard of thrombosis, does this mean that it should never be used in an African country where spontaneous thrombosis is exceptionally rare? And what about chloramphenicol, a drug with rare but important toxic effects in Western countries, that is widely used in the developing world? It is clearly necessary that the potential benefit of such drugs in such countries must not be jeopardized by a national agency controlling that drug for purely national use in the Western country where it is manufactured. Since the major problem that the world faces today is the relationship between the developed and developing world, this is an area of drug control where discussion in international agencies might be encouraged.

Some in the West may say, what does the developing world have to do with us? The Western countries depend to a very large extent on developing countries for their supply of raw materials. The time will come when Transvaal gold is controlled not by Europeans but by Africans, as has happened to other

commodities around the world during the decolonization of the past half century.

But developing countries are also exciting because they are young and new. One is tempted to conclude by returning to Benjamin Franklin in Paris nearly 200 years ago. Watching Monsieur Montgolfier's hot air balloon rising from the Jardin des Tuileries, a friend asked him of what use it was. Franklin made the immortal reply, "Of what use is a newborn baby?"

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ACCEPTANCE OF FOREIGN DATA BY THE FOOD AND DRUG ADMINISTRATION

J. Richard Crout

The U.S. Food, Drug, and Cosmetic Act requires, among other things, that the clinical trials submitted in support of a new drug application (NDA) be "adequate and well controlled" and be backed up by "full reports of investigations" (case report forms). Published papers alone do not ordinarily provide a sufficient evidentiary basis for approval of newly developed drugs in the United States. Clinical trials intended for submission to the United States but performed in foreign countries must be conducted according to the ethical standards of the Declaration of Helsinki or the laws of the country of origin, whichever provides the greater protection of human participants. All controlled clinical trials meeting these conditions are acceptable by the FDA in support of an NDA.

A number of years ago it would have been unnecessary to consider international standards for the acceptance of foreign data from the viewpoint of the Food and Drug Administration. This situation was changed, however—although it took us a few years to discover this fact—by the 1962 amendments to the Food, Drug, and Cosmetic Act. These amendments mandated a number of policy innovations. For purposes of this discussion, by far the most important was the requirement of adequate and well-controlled trials as the scientific technique by which the evidence necessary for approval of new drugs is to be acquired.

Sixteen years later it is easy to see the outcomes of this legal mandate. On the positive side, there has been a complete transformation in the quality of evidence available for decision-making on new drugs. Simultaneously, the general fields of biostatistics and epidemiology have flowered so that today controlled trials are applied to a variety of therapeutic modalities well beyond drugs. As a result, a sound scientific data base for rational decision-making on therapeutic choices is increasingly being built. This revolution in the quality of evidence available to the medical profession for the practice of rational therapeutics can be appreciated at a glance simply by leafing through a few issues of any modern major medical journal and by comparing the general content of papers with that of 20 years ago. Many things have changed, of course, but one

of the most striking is the number and quality of therapeutically oriented clinical trials on a wide range of subjects in today's medical literature.

I believe it is now widely recognized that these scientific gains have been purchased, and will continue to be purchased as is always the case for things of value, at some cost. Clinical trials are expensive, and they take time. Because their results may challenge prevailing practices or conventional wisdom, certain trials inevitably provoke controversy. Because they come under the purview of regulatory bodies, they inevitably become the focal point for differences of opinion, and even formal adversarial legal proceedings between industry and Government. In short, they are important and are properly treated as such by all of us.

General Philosophy and Legal Background

I take it as self-evidently desirable that the members of the international research community have common standards relating to clinical research so all valid data from clinical trials will find broad acceptance by the medical profession and by the regulatory authorities. Although this goal is widely recognized among scientists as a worthy one, it has sometimes been difficult to achieve. I would like to outline, therefore, some of the complexities that confound the acceptance of foreign data by the Food and Drug Administration and to review our policies on this issue.

The central factor determining whether a particular trial is acceptable to a drug regulatory agency, and indeed to any scientist, is its scientific credibility. In many subtle ways we each develop our own biases and attitudes on what we find believable, and nations are no different from individual human beings in this regard. The national attitude in any given country on the type of scientific evidence each finds credible comes about from a complex interweaving of scientific and ethical traditions, legal requirements, and national experience. Those of us interested in international drug trials are, in fact, from different countries with different cultures and medical traditions. So it is natural that we should find ourselves sometimes differing on what we find credible as scientific evidence.

The U.S. Food, Drug, and Cosmetic Act requires that, before a new drug can be approved, the new drug application contain "substantial evidence" that the proposed drug is safe and effective for the intended use. The law further defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling."

In addition, the law states that an NDA must contain, among other things, "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." The requirement for "full reports" has long been considered by the FDA to mean individual case records or case report forms filled out by the investigator. In short, published papers alone or their equivalent in an NDA are usually *not* considered sufficient to fulfill the "full reports" requirement of the law.

Although many nations now have drug regulatory laws requiring evidence of safety and effectiveness, the specific legal requirements for adequate and well-controlled trials and for full reports of investigations is not a feature of the legislation in countries other than the United States.

There has evolved in the United States a set of drug approval requirements that recognizes two different levels of clinical evidence in support of safety and effectiveness:

1. Studies known as *adequate and well-controlled trials* because they meet the requirements for such trials described in our regulations [1]. These regulations require, among other things, that results attributed to the drug must be compared with a control group "in such a fashion as to permit quantitative evaluation," but these regulations do not require, as alleged by some, that all trials be double-blind placebo-controlled trials. The regulations provide for a no-treatment control, a placebo control, an active treatment control, or a historical control, whichever is scientifically appropriate for the drug under study. Thus, as examples, placebo-controlled trials are typical for analgesics, mild antihypertensives, and dermatological drugs, while active treatment controls are common for antibiotics, and historical controls are typical for general anesthetics, cancer chemotherapeutic drugs, and oral contraceptives. A subset of trials in this category are those known internally at the FDA as pivotal studies. These are trials that are adequate and well controlled as described in the regulations and, in addition, are documented by "full reports" of case records. Pivotal studies are therefore, as the name implies, the most important studies for a fundamental judgment on the effectiveness of a drug.
2. Studies known as *supporting evidence*, which means trials that are not well controlled or contain other information such as anecdotal case reports in which no attempt at control has been made.

For the approval of an NDA for a new molecular entity or the approval of a major new indication, we require the application to contain at least two independent clinical trials considered pivotal in support of safety and effectiveness.

We will also accept a single multiclinic trial as sufficient if at least three separate investigators in the trial have enough patients in their individual clinic to demonstrate a statistically significant result within their own series of patients.

I would emphasize that these are the minimum standards required for a demonstration of effectiveness and of safety over the short term. In addition, we usually also require dose-ranging studies in normal volunteers; studies in pharmacokinetics and bioavailability; evaluation of safety and effectiveness in relatively long-term use (usually at least a year) if the drug is intended for chronic use in humans; studies of the drug by both medical specialists and general practitioners; studies in special patient populations such as children and the elderly; studies in association with other drugs that customarily would be given with the new drug in clinical practice; and studies of comparative claims in relation to other similar drugs, if the manufacturer wants such claims in the labeling. The intent is to assure that every newly marketed new entity has a well-rounded, complete package insert as well as evidence supporting safety and effectiveness. In short, much clinical research conducted under phase III of our regulations is done to provide "adequate directions for use" as well as to support the basic safety and effectiveness of the drug.

We also require that *all* evidence related to the drug be submitted, including incomplete studies and unfavorable studies—a requirement we consider essential because it reveals such interesting information as the investigators who lost interest in the drug or found it to be ineffective, as well as those who completed their studies with favorable results.

A typical new molecular entity has thus been studied at the time of approval by perhaps 20 to 50 investigators in 2,000 to 3,000 patients. In the case of drugs used for the treatment of rare diseases, approval has been granted on the basis of studies in relatively few patients, but this is the exception rather than the rule. Most NDA's are supported at the time of approval by several controlled trials of the pivotal type, additional controlled trials and papers taken from the medical literature, and other information that qualifies as supporting evidence.

It is true that we have accepted on occasion some trials published in the literature as providing "substantial evidence" of safety and effectiveness even though the case records underlying these trials were not available. This has occurred, however, mainly with already marketed drugs where the case records supporting older published studies are literally not available or where the number and quality of independent reports in the literature is sufficiently high that there is little reason to question the validity of the studies.

Approval of a drug or a major new indication on the basis of published papers alone is, however, the exception, not the rule. Our customary approach, and certainly the standard approach with new indications studied under the investigative new drug process, is to require at least two pivotal studies that are well-controlled *and* documented by case reports. This does not mean that we ignore well-controlled studies published in the literature that lack case records

or uncontrolled studies submitted as supporting evidence. But it does mean that such studies are used for somewhat limited purposes, such as the extension of an indication to a new patient population (e.g., children, the elderly) or the providing of new information in the package insert on mechanism of action, metabolism, or adverse effects.

Acceptance of Foreign Data

We are frequently told that the FDA has a long-standing reputation of not accepting, for purposes of new drug approval, clinical trials conducted outside the United States. This is not a correct statement of FDA policy, although I can readily see how this impression of our policy arose.

To set the record straight, I emphasize that the FDA does not have a policy of rejecting foreign studies merely because they are foreign and has never had such a policy. There is no scientific basis for assuming that the quality of clinical research depends on the country in which it is conducted, and FDA policy recognizes no such national distinctions. However, our policy of accepting as pivotal studies only those trials supported by case reports has clearly worked against the acceptance of many well-controlled trials conducted in foreign countries. The issue here, however, is not the country of origin or the scientific quality of the trial, but the degree to which the findings can be documented by case reports.

We are aware that some investigators consider the providing of individual case report forms as, at best, an odious task or, at worst, an improper reflection of their scientific integrity and honesty. This is admittedly a difficult and sensitive problem, but in our experience not an insurmountable one. In fact, objection to this type of documentation tends to disappear as good investigators gain experience with the system. Good scientists will make every effort to assure worldwide acceptance of their work if they understand the reasons.

The FDA requirement for individual case records or report forms derives, regretfably, from unfortunate practical experience. We have simply seen too many studies in which the senior investigator delegated critically important decisions to junior subordinates and failed to report this in the published paper. Case records may reveal that some patients selected for a study did not meet the entrance criteria stated in the protocol, that some failed to take medications on the scheduled days, that they failed to have essential laboratory studies done at the proper time, that they dropped out or failed to return for visits critical to the study, that they took concomitant medications which might confound the results, or that breakdowns occurred in the randomization or blinding processes. When data are retabulated to take such discrepancies into account, the statistical evaluation of the data and the results of the study may be profoundly altered. Problems of this type are not uncommon in studies submitted to the FDA. Unfortunately, such problems can occur even in studies

conducted by eminent investigators at well-known institutions and in studies sponsored by large, respected drug firms.

It is important to recognize that well-considered protocols and case report forms serve an essential scientific purpose and do not exist merely to fulfill regulatory requirements. Such forms can specifically stimulate the systematic obtaining of essential information on each patient as the study progresses. These forms must be filled out immediately and be monitored continuously by the senior investigator and by the drug firm to assure completeness and accuracy. Anything less cannot properly be considered as well-disciplined scientific research. Clinical trials are inherently complex and error-prone, and their proper execution requires a strong sense of organization and attention to detail. Case report forms, along with a good protocol and effective monitoring, promote the disciplined conduct of a clinical trial. In addition they provide a means of auditing the study later.

To make these policies clear, the FDA has published regulations relating to the acceptability of international clinical research in support of an NDA [2]. These regulations state that adequate and well-controlled trials supported by case records will be accepted on the same basis as such trials conducted in the United States. These trials must be conducted according to the ethical standards of the Declaration of Helsinki or of the laws of the country of origin, whichever provides greater protection to human participants.

In recent years we have been impressed with the quality of information from foreign countries submitted by drug firms under these regulations. Foreign data now constitute the bulk of studies available in many NDA's submitted for approval in the United States. A question frequently asked of the FDA is whether we are prepared to approve an NDA *entirely* on the basis of foreign data collected under these new international research regulations. Our current regulations state "except when the disease for which the drug is being tested occurs with such frequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States"[3]. Although there is no intrinsic scientific reason why certain drugs could not be approved solely on the basis of foreign data, we believe it premature to consider such a policy at this time.

In justifying a requirement for some domestic trials, I can only return to my comments at the beginning of this chapter about credibility. In our modern era of public concern about drug safety, it would simply not be credible for the FDA to approve for marketing a new molecular entity that has never been evaluated by any domestic investigator or practicing physician. It is customary for many countries, especially those with strong drug laws and large markets, to require at least some domestic testing of new drugs before they are approved, and the United States is no exception to this worldwide practice. Until we have considerably more experience, it is likely that most of the foreign drug studies accepted in support of an NDA in the United States will be

phase I and phase II studies, or selected phase III studies. I suspect that some portion of phase III will need to be done domestically for some time to come.

International Harmonization

Finally, I would like to comment on the international harmonization of approval decisions on drugs. If these decisions could be left to scientists and physicians alone, I suspect that international decision-making on drug approvals would be more consistent worldwide than is now the case. However, a variety of other factors enter into decisions besides the scientific evidence at hand. In particular are the marketing desires of the sponsor, the legal standards to be met, and the public procedures to be followed, all of which differ widely among the nations of the world. On the matter of credibility and public acceptance, these legal standards and procedures are not easily translated from one country to another. Nevertheless, those of us in the business of regulation and drug control must make every effort to reconcile such differences. To do otherwise is to promote waste in research and confusion of the drug industry, the medical profession, and the public.

As a suggestion on how to improve harmonization, I believe we must recognize the major reasons for our differences are largely nonscientific. They derive instead from differences in legal standards, attitudes, and the decision-making processes of Government in our respective countries. I would not deny that gains can be made at the technical level from international consensus on such matters as toxicology requirements and methods for the evaluation of safety and effectiveness. But only partial harmonization of approval decisions can result from such technical reconciliation. It is most important that we come to understand in detail each other's laws, each other's decision-making processes, and each other's biases.

References

1. Code of Federal Regulations, Title 21, Food and Drugs, Section 314.111.
2. Code of Federal Regulations, Title 21, Food and Drugs, Section 312.20.
3. Code of Federal Regulations, Title 21, Food and Drugs, Section 314.1(c). Item 12c of form FD-356H.

DISCUSSION

George T. Curlin

Chief among the subjects discussed was the problem of how to monitor adverse reactions to new drugs; Dr. Crout was the primary respondent. He was asked if the FDA should not scrutinize the data as carefully from a safety aspect as from the aspect of efficacy in those situations when the information appeared important enough to warrant consideration of relabeling. Dr. Lasagna thought the list of shortcomings in the quality of data, failure to follow protocol, etc., mentioned by Dr. Crout as problems in initial applications were also seen in the restudy of oral hypoglycemics, for example. He asked if the FDA should not scrutinize those firsthand reports with the same intention of looking at the quality of the data on the negative side as on the side of claiming benefits.

Dr. Crout replied that while the University Group Diabetes Program (UGDP) study, which was audited by the FDA, contained deficiencies in the data, the general nature of the incentives for drug companies to pursue possible adverse reactions ensured a fairly complete job of reporting. The FDA, therefore, audits selected studies as a matter of principle. In pursuing this line of inquiry, Dr. Weatherall asked if anyone had any ideas toward developing a national system of reporting adverse drug reactions in general. She acknowledged that workers in the United Kingdom found it difficult to give answers to these questions because it was difficult to state if a reaction were due to the drug or were a general consequence of the illness or the environment. Dr. Crout felt that no one had attacked this problem successfully. Although the United States has a spontaneous adverse drug reaction reporting system similar to that used in the United Kingdom, the drug companies themselves handle the problem to a greater extent in the United States than in the United Kingdom. Therefore, in the United States there is no stable of physicians working for the counterpart of Bill Inman, and as a consequence our contacts with physicians are different from those in the United Kingdom.

Although there are epidemiological surveillance programs of adverse drug reactions in the United States such as the Boston Collaborative Drug Surveillance Program, the Drug Epidemiology Unit at Boston University, and the teratology monitoring activity at the Center for Disease Control (CDC), none of these could be considered a comprehensive national adverse drug reaction system. Because of a network of investigators wherein everyone strives to remain in touch with others, more is happening in this field than the practicing physician knows about. In the United States the reporting system is not so much of a problem as the assembly of reports and the feedback of this information to practicing physicians. Dr. Crout felt the United Kingdom did better

than the United States in this regard, but Sweden probably did better than either country.

The problem of the cost of following up reports of adverse drug reactions was mentioned as being beyond the means of small pharmaceutical firms; this situation makes government participation in the activity more likely. In the United States the FDA and CDC occasionally send physicians to follow up a report of an adverse drug reaction, but Dr. Crout admitted the U. S. Government does not do it very well. Almost all reactions under consideration occur in the first few years of marketing when the drug companies are very active and expert in following up reports. They are required by law to do this and are further stimulated to be aggressive by the threat of litigation, which is a much greater force in the United States than in the United Kingdom. The U.S. Government's job is to understand and deal with the bias often contained in such reports when they are received from the industry, for the information frequently minimizes the problem. Dr. Crout felt the actual legwork is done fairly successfully by industry, and he was not personally in favor of investing more government resources in this area.

Professor Vere suggested the nagging problem of unsuspected adverse drug reactions lay behind all the safety problems under discussion. Most of the reporting schemes depend on the doctor's reporting suspected adverse reactions. In the United Kingdom investigators are beginning to be very uncomfortable with the specter of unsuspected adverse reactions, a feeling increased considerably by the practolol case. Under consideration in the United Kingdom is a plan to initiate a recorded release type of scheme wherein doctors would report all adverse events that might follow exhibition of a drug under surveillance. The crunch in this scheme is the tremendous expense; it is so large that Government will almost surely have to be involved at some point. Dr. Crout agreed the problem of the unsuspected adverse reaction is serious. Although the FDA has looked into this problem extensively and is actively exploring solutions, to his knowledge no one has yet found a cost-effective way to detect previously unsuspected adverse drug reactions (thalidomide and practolol are prime examples). Dr. Crout feels we may be left with considering such reactions a societal cost of new drugs from a cost-effective point of view. If this is the case, the public should be informed.

A member of the panel asked Dr. Crout to respond to Professor Booth's comment in his presentation about the international impact of domestic drug regulations. The highly technically developed countries were noted to bear some responsibility for the availability as well as the development of new drugs that have utility in developing countries. A recent case in point concerned a depot preparation of a progestogen for use as a contraceptive. Although this product has been marketed for years in the United States for use in the management of specific cancers, it was not approved for use as a contraceptive in the United States because of the lack of a suitably identified target population

and its cancer risk, which did not justify use where other contraceptive methods were available. All agreed, however, that its use could be justified in many developing countries where different health and demographic situations pertain. The FDA ruling, therefore, seriously affected the availability of this drug in places where its use could be justified. Dr. Crout acknowledged that regulatory agencies in the highly developed countries have the power to "kill" a drug around the world, so to speak, and one must recognize the fact that safety actions taken by agencies such as the FDA have far-reaching effects. There are times, however, when we do not want the power to operate in this way; and the example cited above may be such a case. Both the United States and the United Kingdom have decided not to approve this drug for use as a contraceptive in their own countries, but it may not be best for this ruling to spread throughout the world. Dr. Crout commented that there is no solution to the problem except to say clearly in public statements and in official comments to organizations such as the World Health Organization that we hope this does not happen. In countries with a population problem, maternal and child health problems, and related problems of limited life expectancy, Dr. Crout said marketing the drug as a contraceptive was justified.

In dealing with the impact of domestic laws on the availability of drugs in the international setting, Dr. Crout pointed out that the new drug law currently under consideration by the Congress contains some interesting provisions bearing on this problem. Under the existing law, a drug cannot be exported from the United States unless it is approved for the same use in this country. Therefore, injectable progestogen cannot be exported for use as a contraceptive. Under the new law, however, an export license can be obtained for any drug if requested by another country. This is a very controversial section of the new law; everyone acknowledges this provision to be a double-edged sword. Although there may be losses as well as gains from this provision of the new law if it is passed, the FDA will try to enforce the new law to produce gains, not losses. A safety aspect override provision is included in the new law, but it is understood the FDA is to exercise its authority under the override provision with careful judgment.

Professor Booth was asked if his term "preventive illness" was not a bit illusive. He had mentioned having enough patients with preventive illness in hospitals to practice on, and this statement in itself indicated the diseases are not, in fact, being prevented although they might be preventable in a theoretical sense. This comment allowed Professor Booth to reemphasize the point that we are being pressured into diverting increasing amounts of scarce resources from acute care into prevention when we do not yet know how to prevent most diseases. Somewhat on the lighter side, Professor Booth commented that there were but two areas in our experience in which preventive efforts were successful: first, in the areas in which legislation was brought to bear on a problem, such as the U.S. legislation of speed limits; and second, by giving 6 years of medical education to someone and encouraging him to stop smoking. He

labeled the rest of our performance in prevention as ludicrous and not very effective, terms which are not necessarily mutually exclusive.

An effort to draft uniform technical information about the side effects and indications for use for drugs promulgated for the developing world, much as they are in the developed world, was one area of consideration for international standards. A factor explaining why many drugs are abused in the Americas is a lack of understanding among practitioners of the guidelines of indications, contraindications, and side effects of drugs imported in quantity by developing countries. The participants did not pursue this suggestion, and there were no other concrete suggestions for international cooperation.

In response to a question about the comparison of time for a new drug to be approved in the United States and the United Kingdom, Professor Lawrence said the mean time in the United Kingdom fluctuates. The mean time for a clinical trial certificate is 3 to 4 months, and the time for a product license is 6 months, assuming all goes smoothly and the application is not returned. The difference in time to obtain approval as a factor in the decision of many drug companies to conduct clinical studies in the United Kingdom was not addressed directly by the participants.

Dr. Crout closed the discussion by supporting the call for joint efforts to place escalating new drug regulations in proper perspective and suggested that the pharmaceutical industry be enlisted in the process. He commented that industry must be more specific than they have been previously in documenting the cost of each regulation. For example, comments to the effect that it requires $55 million to work up a new drug are not likely to produce any rational movement in a complicated process to reduce regulation. Accurate data of the cost of a specific regulation (such as 6-month toxicology data, for example) would be welcomed, however, by reasonable people who can then reconsider the cost and the benefit of such a regulation in the public process.

GENERAL SUMMARY STATEMENT

Kenneth J. Ryan

As I faced the unenviable task of recounting the presentations and exchanges of our 2 days of meetings, a colleague just reminded me: "If this conference was good, it should require no summary, and if it was bad, it shouldn't be summarized." I'll opt for a middle ground and try to highlight a few salient points.

For the most part, ethical concerns in clinical research have in the past been based on the medical practice model and the rectitude of the individual physician-investigator. This has not been completely sound in either theory or practice. Although problems have been few relative to the wide extent of clinical research, when problems have occurred, they have attracted the wide attention of the public and governmental regulatory agencies.

In Great Britain, the experience with thalidomide and the publicity associated with Owen's book, *In Sickness and in Health,* raised the general awareness that all was not well. In the United States, the creation of our national commission was spurred on by concerns over research on aborted fetuses, prison research, psychosurgery, research in mental institutions, informed consent for sterilization, the Tuskegee study of untreated black syphilitics, and the clinical use of such drugs as diethylstilbestrol and medroxyprogesterone. We in the United States had already had our own problems with drug safety many years before thalidomide, resulting in FDA regulatory oversight.

A lesson from these experiences is that when the caretaker is also an investigator, there is at least the semblance of possible conflict. The "paternalistic physician" trying to avoid upsetting patient-subjects has in the past been the sole judge of what to disclose and when to ask for written informed consent. In 1966, the U.S. Public Health Service instituted the requirement that all federally supported research be subject to a peer review committee (institutional review board) with outside representation, as well as an evaluation of risks and benefits and adequacy of the informed consent process. This has left untouched any real surveillance of innovative practice and the unapproved usage of drugs where risks may be higher than in carefully designed research

protocols. In any case, most in the United States agree that the institutional review board function for research has filled an important need and should be maintained and strengthened. It is possible that protection of research subjects by such a review process should be used as a model to protect recipients of medical care rather than the reverse, as was the case in the past.

The "window" referred to by Dr. Levy as the optimal time for testing the safety and efficacy of a medical or surgical procedure is an important concept. On both sides of the Atlantic, medical activities have sometimes crept into practice without adequate justification. One then hears the comment that it would be "unethical" to do a controlled study and deny some patients the benefits of the putative therapy. On the contrary, it was "unethical" to allow activities to creep into practice for which clear risks and benefits were not validated. One need only mention cardiac bypass surgery, hypophysectomy for diabetic retinopathy, or the use of oral hypoglycemic agents to illustrate the point.

In this regard, the United Kingdom, with its National Health Service, is in a better position to support and monitor the actual practice of medicine, innovative therapy, and appropriate clinical research than this country, where the activities are largely in the private sector.

We have had a heated discussion on informed consent. In some instances withholding information from both the subject and relatives had been defended to protect them from undue distress. Although special situations may seem to require this, it is a troubling practice. One should not reinstitutionalize the old paternalism in the guise of treating kind and concerned. In the case cited of children with leukemia, the parents may not be able to choose between two forms of imperfect therapy or palliatives, but, at the very least, should they not know that there are no accepted curative therapies (otherwise, why the study?) and that clinical trials will be randomized between two reasonable alternatives with respect to risk and benefit?

In the case of patients in an intensive care unit, should the relatives not know that you are constantly studying ways to deal with emergencies and that alternative forms of care are being studied? Subjects and/or relatives have a right to know that research is being performed. The burden of proof remains on the investigator who withholds information, and with the review board that countenances it. More often than not, information must be adequate to respect the decision-making and autonomy of the individuals involved.

I also deplore the overly technical informed consent documents, but the alternative is clear and relevant disclosure, not its complete absence.

It is impossible to deal with all the issues raised; I highlight as the most important concerns the need for a peer review process for research and practice, the timely validation by appropriate clinical research protocols of innovative therapy before it becomes practice, and adequate disclosure to subjects and/or their relatives. The public we serve and the Government that supports our endeavors deserve no less.

ANALYTIC SUMMATION

Miles Weatherall

On analyzing the proceedings, it seems appropriate to mention some aspects of research with human subjects that have *not* been presented here, but should not be forgotten in taking stock of the subject. We have not talked much about studies on normal volunteers, and we have not heard any volunteers express their opinions about control on their activity. We have also heard no comment from a doctor or research worker from the developing or third world on its problems as they relate to research in human subjects. I will come back to these points, but first let us consider what we have done.

Essentially we have been reviewing our own responsibilities as doctors and research workers. These responsibilities have grown with the growing power of science. They frighten us, and they frighten the community, which needs to be assured that power is well used.

To control this growing power, it is essential for the doctor to retain his sense of responsibility and trustworthiness: for him to be seen as always acting responsibly. It is necessary also to educate the community, so the actions of responsible doctors are understood. A doctor has a responsibility to acquire knowledge as well as to treat: to experiment when he does not know what to do, and not to experiment when he does know. And he should acquire knowledge with the same meticulous care for the individual as he shows in treating the individual patient. Neither the community nor the doctor always sees these simple responsibilities clearly. If this conference has helped to make them more clear and more widely understood, it has served a most valuable purpose.

Some doubts, which I share, have been expressed about "dinosaur" trials. If it needs more than 100 subjects to show an effect, either it is a mighty small effect, or the residual variance is shockingly uncontrolled. Monitoring for rare serious toxic effects is another matter; if an effect occurs in only 0.1 percent of patients, at least 5 to 10 thousand patients must be studied to form an approximate estimate of its incidence and of its severity. But monitoring should be achieved with less formidable cost and use of resources than planned therapeutic trials on the same number of patients.

Doubts have been raised also about informed consent and about ethical committees. The need to restrain unfettered enterprise is not at question, but the processes of amateur advisory agencies and bureaucratic blight are not automatically beneficial. Might it be that setting up a committee is a way of shirking a personal responsibility? There are good and bad reasons for creating a committee, but one who does so should question oneself as to whether it is being done not to give members their rights but to abdicate one's own duties.

Finally, I mentioned some points of view that have not been discussed but might serve as a frame in which to set the work of these useful days. First, about volunteers, are there not a considerable number of well-informed people, particularly working scientists, who will gladly submit themselves to hazardous procedures, knowing the risks of an experiment as well as anyone? What would such courageous and admirable people say if they were prevented from contributing to human welfare by the deliberations of a well-meaning ethical committee? Second, any of us who has studied the subtleties of human interactions ought to ask "How reproducible are the judgments of such committees?" Third, from the developing world a question might come as follows, "How many doctor-hours, doctor-years, are being expended in the niceties of ethical decisions in rich countries, while we have only 1 doctor to cover 10,000 square miles or 80,000 patients?"

I close with these thoughts as part of our collective self-discipline and sense of responsibility to all patients and all people everywhere.

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